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ALIMENTARY CANAL

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HARELIP AND CLEFT PALATE*

G. B. NEW

Harelip and cleft palate are congenital malformations due to the failure of union of the parts that form the lip and the palate. The palate is formed from the globular and the maxillary processes of the mandibular arch; the lip is formed from the globular, the lateral nasal, and the maxillary processes. While several theories have been advanced for the lack of fusion of these parts, no definite cause seems to be known.

Heredity may have some bearing on the condition, since in a small percentage of cases a hereditary tendency to deformities is noted in families. Sometimes a parent and child are deformed, and again, different children in the same family may have harelip and cleft palate. In 14 per cent of the cases of harelip and cleft palate seen in the Mayo Clinic there is a family history of the occurrence of the condition. In 4 per cent a brother or sister has a harelip or cleft palate, and in 10 per cent the parents or ancestors have been so deformed. In one family three children had harelip and cleft palate.

Many types of both harelip and cleft palate are seen. The lip may be fissured on one or both sides, and there are all grades of deformity. In a slight deformity the musculature of the lip may be thinned out, a groove being formed from the nostril to the vermilion border, with a slight notch in the lip, or there may be a complete unilateral harelip with flattening on one side of the nostril and separation of the alveolar process. The double complete harelip presents a marked deformity in which the nostrils are flattened. The filtrum and the premaxilla extend forward and are attached to the tip of the nose. The palate also may vary in the type and the extent of the cleft. The alveolar process may be notched, or the cleft may extend completely through the hard and soft palates; the uvula may be bifid or the soft palate may be cleft. The parts of the palate may be widely separated, as seen in a double cleft palate.

The age at which the child with a harelip and cleft palate should be operated on, and the operation which should be done first, are much debated questions among the various men performing these operations. Moreover, there are many types of operations for these deformities. I will not attempt, at this time, to discuss the advantages and disadvantages of different methods, but I will describe the procedure which, with slight minor modifications from time to time, has been employed for many years at the Mayo Clinic.

We prefer to close the lip first when the child is between three and four months old, if he is gaining weight and doing well. Children are operated on earlier than this, but results are not so satisfactory. From three or four days to a week before the operation the child should be fed with a spoon or dropper, to accustom it to this method of feeding, since, of course, after the operation it is not allowed to nurse from the bottle or the breast. When there is a cleft of the alveolar process, as in the complete single harelip, the lip is brought together over it, but no attempt is made to approximate the alveolar process. The same procedure is used in the treatment of the premaxilla. In a case of double harelip the lip is brought together over the premaxilla and its normal rounded appearance is maintained. If the alveolar process is forced back in the single harelip, or if the premaxilla is removed in the double harelip, or a wedge-shaped piece is taken out of the vomer and the premaxilla forced back, the lip will be flattened and it will be almost impossible to correct the deformity. When united, the lip gradually presses back the alveolar process or premaxilla into its normal position, giving the normal rounded contour to the face and the correct alinement to the teeth.

A satisfactory cosmetic result is obtained only when the nostril has been shaped to correspond to the normal side. To do this the nostril should be made a little smaller than seems best at the time of the operation, since the cartilage tends to spread a little within a few days. It is also essential that a line drawn underneath the alæ of both nostrils shall be at right angles to the midline of the face. The vermilion border must present a continuous line without a notch, and there must be as little scarring as possible on the outside of the lip. To prevent the scarring it is best to avoid tension sutures which pass through the skin on the outside of the lip. The lip and cheek on both sides should be well freed from the underlying bone, so they will fall together readily without tension.

The time for closing the palate is when the child is from a year to a year and a half old, before it has begun to talk. Many operations are performed much later, however, with quite good functional results. Adults from twenty to thirty years of age have had their palates closed, and the functional results have been very good. If the lip has been approximated at the proper age, the alveolar process will have become approximated; the cleft of the rest of the palate will thus be narrowed and made easier to close.

The edge-to-edge approximation or the Langenbeck operation is the operation of choice for the closure of cleft palates. With this method as much of the palate is approximated as may be accomplished without tension at the one operation, the remainder being closed later either by an edge-to-edge method or by turning a flap. Failures are frequently due to the attempt to close too much of the palate at one time, in such cases tearing out of the stitches results. When the palate begins to pull out with tension, the tear may often extend into the part of the palate that would otherwise have held together. It is sometimes possible to close a soft palate with the edge-to-edge approximation method, but the hard palate may require a flap operation. We do not like to use the flap method primarily except in certain wide clefts, usually double clefts that cannot be closed satisfactorily in any other way.

It would seem that the most important factor necessary to success in operations on cleft palates is a thorough knowledge of the blood supply. In making the lateral incision it is essential that they be made as close as possible to the teeth or to the alveolar process so that the main branches of the great palatine artery may not be injured.* It is also necessary to thoroughly free the mucoperiosteal flaps. In doing this the posterior margin of the hard palate must be freed from the soft palate so that the two portions of the palate may be approximated without tension.

In closing a cleft of the soft palate the same principles hold good as are used in closing the complete cleft palate. Also in these cases the posterior margin of the hard palate should be freed from the soft palate.

TECHNIC OF HARELIP OPERATION

The child is anesthetized with ether by the drop method, and is kept asleep with chloroform administered on a gauze sponge. Older

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* These are not the long lateral incisions to which the term is usually applied, but are just long enough to admit the palate elevator for elevating the palate.
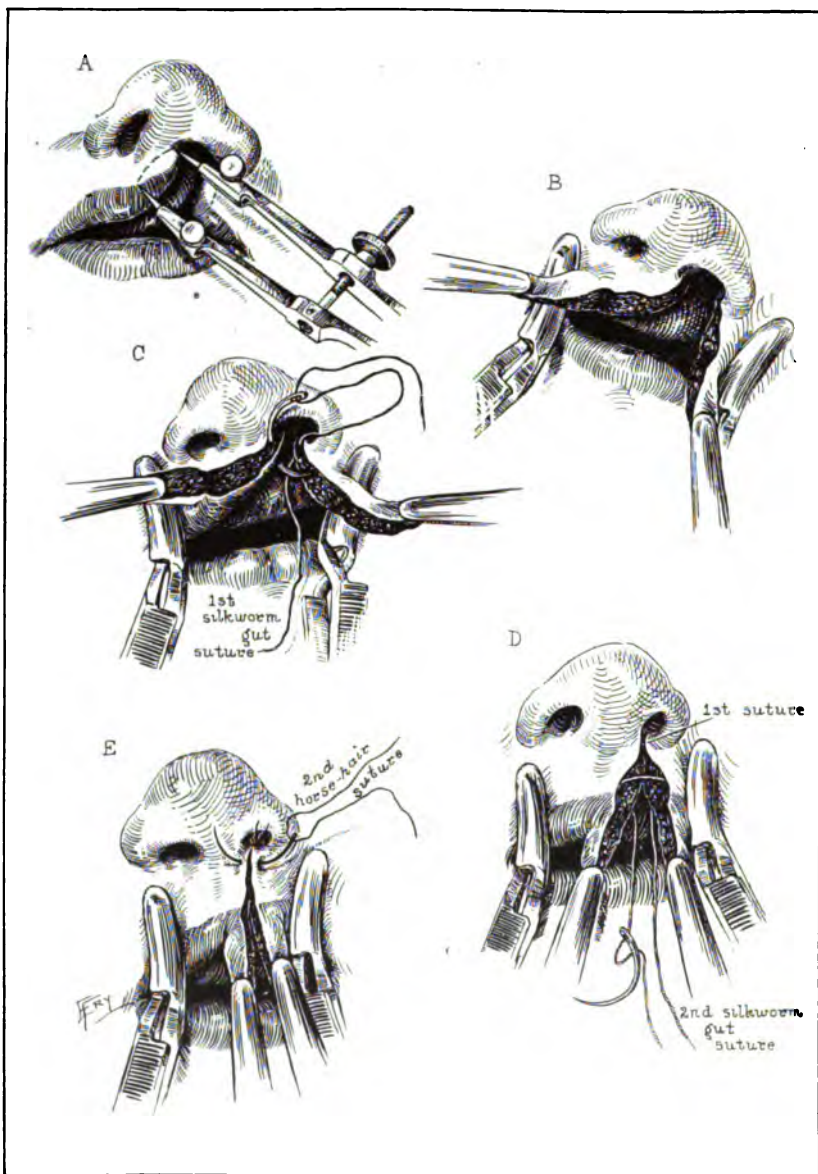
Fig. 1.—A, The calipers determining the length of lip on either side and the points on the vermilion border to be approximated.   B, The mucocutaneous margins have been pared and the lip freed from the bone.   Small clamps on either side of the lip to control bleeding.   C, First silkworm-gut suture inserted from the inside.   It does not pass through the skin.   D, First silkworm suture tied, approximating the nostril.   The second silk-worm suture in place.   E, Horsehair sutures approximating skin.

children are given ether vapor through a cannula at the side of the mouth.

In operating on the single harelip a point is selected on the median portion of the lip, at the vermilion border, where the lip should join the opposite portion. The location of this point depends on the type of the lip as regards its thickness and the amount of tissue present, and on the experience of the operator. A small nick is made with a knife in the skin at this point. Calipers are then used to measure the distance from here to just inside the ala of the nose on the same side. This distance fixed, one point of the caliper is placed just inside the ala of the nose on the outer side, and the other point at the vermilion border. In this way the points of the vermilion border which are to be approximated are definitely fixed, and the two margins to be approximated are made the same length. Thompson, I believe, was the first to suggest the use of the calipers for the purpose of measuring definitely the free margins to be approximated.

Fig. 2.—F, The lower lines show approximately where the parings are cut. G, Lip completed with horsehair sutures. Note the fullness of the lip along the suture line and the slight pouting of the vermilion margin.

A curved incision is made through the skin on either side, the mucocutaneous border being pared from immediately within the nostril down to the fixed points on the vermilion margin. The

parings are left long, and their ends are fixed with small stomach clickers. The use of traction and pressure, applied on either portion of the lip, along with small clamps applied about an inch back from the freshened margin, is the best method of controlling bleeding. It is essential that

Fig. 3.—(192255.) Harelip, incomplete, before operation.

Fig. 3a.—(192255.) Same as Fig. 3 after operation.

Fig. 4.—(177516.) Harelip. Note marked flattening and deformity of nostril.

Fig. 4a.—(177516.) Same as Fig. 4 after operation.

the lip portions on either side should be well freed from the bone so that the two portions fall together quite readily, but it is not advisable to cut into the septum to do this.

Tension sutures of silkworm are used. The first suture is placed just

inside the nostril, being passed in through the mucous membrane and brought out beneath the skin on the outer portion of the lip, just inside the ala of the nose. It is then put in again just beneath the skin and passed out through the mucous membrane on the central portion of the

Fig. 5.—(181430.) Front view. Note un-
sightly notch and flattening of nostril.

Fig. 5a.—(181430.) Same as Fig. 5. Side view.

Fig. 5b.—(181430.) Same as Fig. 5. Front
view after operation.

Fig. 5c.—(181430.) Same as Fig. 5. Side view after
operation.

lip, close to the septum. When this suture is tied, the flattened nostril is rounded up into shape. Two silkworm sutures are used to approximate the lip and these are tied on the inside of the lip. As they do not pass through the skin there is no scarring from the tension sutures. Horsehair sutures are used to approximate the skin. After the upper two-thirds of the lip is approximated, the surplus of the pared edge is trimmed off and the lip closed with horsehair. In order to avoid an unsightly notch it is necessary to leave a little excess of tissue at the lower part of the vermilion border so that the lip pouts a little. This is best accomplished by leaving the parings long until most of the lip is closed, when one is better able to judge how much should be excised (Figs. 1, 2, 3, 3a, 4, 4a, 5, 5a, 5b, and 5c).

Technic of Cleft Palate Operation

After the child is anesthetized the head is brought over the end of the table and allowed to rest in the lap of the operator, who sits on a stool at the end of the table. A Whitehead mouth-gag is used, and with a tongue depressor the tongue is lifted, giving a good exposure of the palate.

In closing a single cleft palate an incision is made on either side close to the alveolar process or teeth, and carried down to the bone. It is just long enough to admit a thin, blunt periosteal elevator. By keeping the incision close to the alveolar process or teeth the posterior palatine artery is avoided. Injury to this artery may interfere with the blood supply of the flap.

With a periosteal elevator the mucoperiosteum is elevated over the entire hard palate down to the cleft. With a scissors the soft palate is liberated from its attachment to the posterior margin of the hard palate, and the entire mucoperiosteum of the palate margin is freed as much as possible. The soft palate is attached to the hard palate margin by the palatine aponeurosis, and there is no danger of cutting any important vessels at this point. The freeing of the posterior margin of the hard palate from the soft palate is very important either in closing a cleft of the soft palate or in a complete cleft palate, since it is advisable to sever this aponeurosis in order to approximate the margins of the palate. The mesial margins of both sides of the palate are freshened by fixing the uvula with a stomach clicker and trimming the mucous membrane from the free margin with a scissors or knife. The procedure is begun posteriorly and extended forward.

Silk sutures are used, the first one—a mattress suture—being placed at the juncture of the hard and the soft palates. From this point the rest of the soft palate and uvula is closed by interrupted sutures along the oral and nasal mucous membrane. By leaving the ends of the

Great
palatine a.

Branches to
soft palate   Branch anastomosing
and tonsil   with ascending palatine a
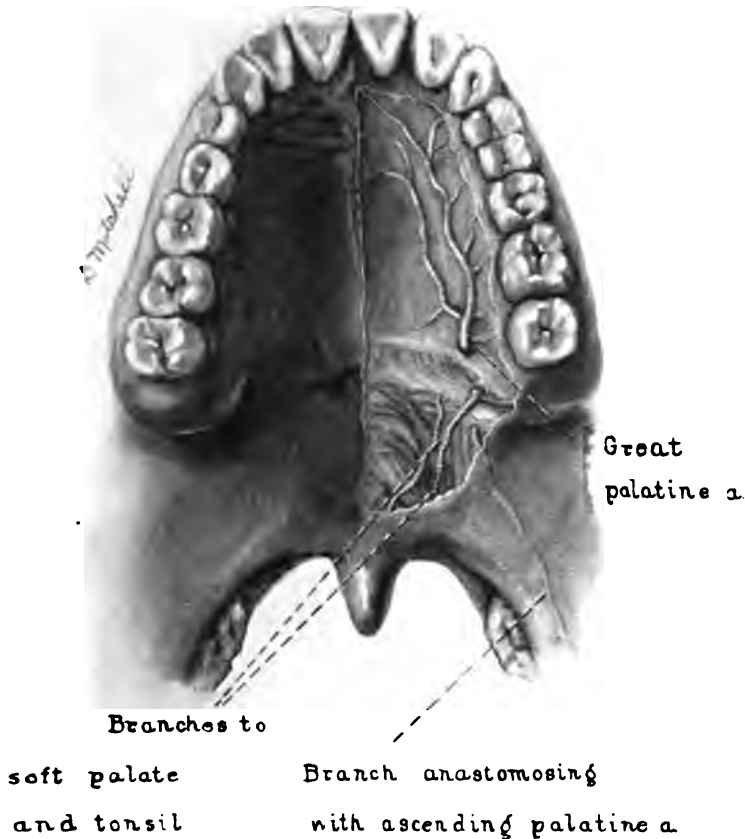
Fig. 6.—Blood supply of the palate. Note the relation of the great palatine artery to the alveolar process, also the branches to the soft palate.

sutures long and fixing them with forceps as they are put in the uvula is brought up into the mouth and the insertion of the sutures is made easier.

The completion of the closure of the hard palate is accomplished by mattress sutures, usually two, and occasionally an interrupted suture.

It is best not to use too many sutures in approximating the margins of the palate; if the tissues have been thoroughly freed, they usually come together of themselves. If it is necessary to employ the flap method to close part of the palate, the technic employed by Lane, or that of turning a flap and suturing it under the opposite side of the palate with mattress sutures, is used (Figs. 6, 7, and 8).

Fig. 7.—Blood supply of the palate. Note the position of the great palatine artery and its anastomosis.

POSTOPERATIVE CARE

Following the operation for harelip a strip of adhesive plaster is placed across the cheeks over the nostril, and another one across the cheeks over the chin, in order to relieve the tension on the sutures in the lip. Horsehair stitches in the lip are removed in about four days and silkworm stitches in about a week. In cases of cleft palate the patients

are not allowed to have anything but fluids, which are given with a spoon or a dropper. The sutures usually slough out, but if some remain at
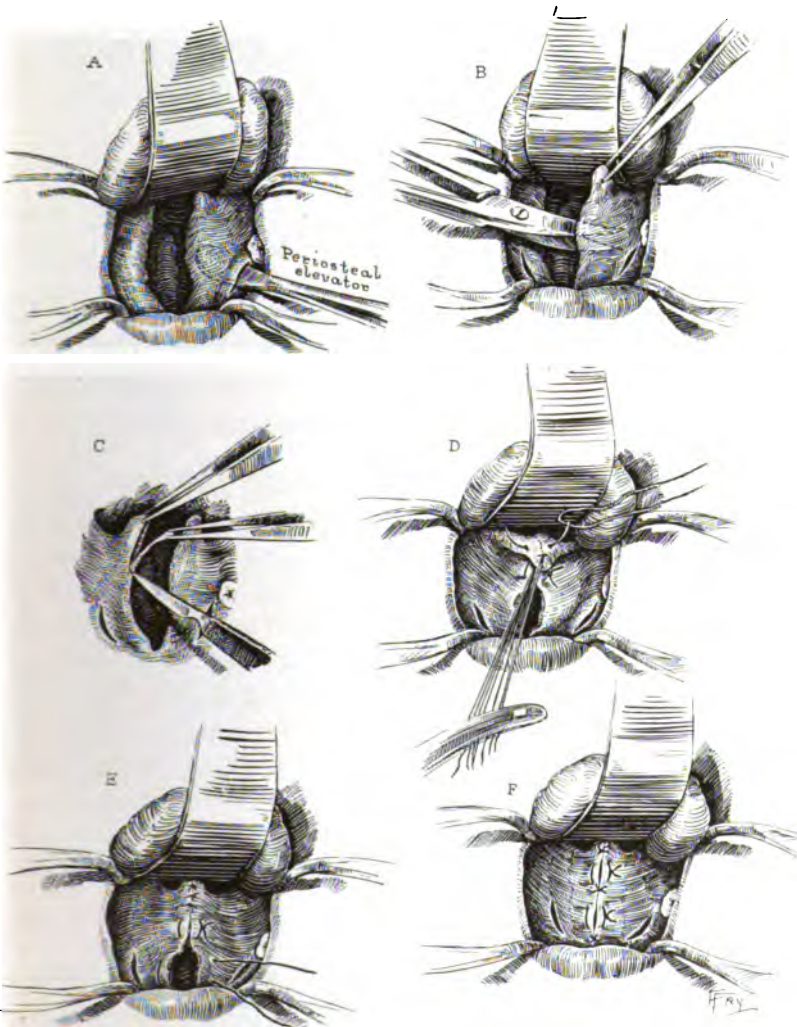
Fig. 8.—A, Periosteal elevator freeing mucoperiosteum from hard palate through incision in alveolar process. B, Scissors separating posterior margin of the hard palate from the soft palate. C, Paring the mesial margins of the palate. D, Soft palate and uvula approximated. Sutures left long and fixed with forceps. Suture in place on the nasal surface of the uvula. E, Soft palate completed. F, The palate completed. Mattress sutures and occasional interrupted sutures.

the end of ten days or two weeks and the child is leaving for home, they are removed.

CARTILAGINOUS TUMORS OF THE LARYNX*

G. B. NEW

Cartilaginous tumors of the larynx occur but rarely: only 38 cases have been reported in the literature. In 1900 Alexander reported 29 cases tabulated since 1834, and in 1909 Mansfeld reported 9 cases. In addition, I have been able to collect 8 cases from the literature and 1 of my own, making 47 in all. In 3 of Alexander's cases there was general hypertrophy of one or more cartilages of the larynx; it seems questionable, therefore, whether these cases should be classified with true laryngeal tumors.

The first case report was published by Froriep in 1834. In this case a large cartilaginous tumor on the left side of the larynx, a smaller tumor below the cords on the right side, and a third on the anterior surface of the posterior part of the cricoid cartilage, were found at postmortem. After the introduction of the use of the laryngeal mirror in 1859, many laryngeal tumors, previously considered rare, were noticed, and the first clinical case was reported by Türck in 1863. The patient died the day following the examination, and at necropsy a tumor of the cricoid cartilage was found. In 1888 Bruns collected 10,747 case reports of laryngeal tumors and found only 14 cases of cartilaginous tumors. The first work of importance on cartilaginous tumors of the larynx was not brought out until 1900, when Alexander's very thorough study on the subject was published.

Virchow classified such tumors as: (1) Ecchondromas, that is, cartilaginous tumors that are an outgrowth of the mother substance, like the branch of a tree, and do not invade the original tissue, and (2) enchondromas which develop from a non-cartilaginous matrix. If this classification is accepted, all cartilaginous tumors of the larynx would be classified as ecchondromas, as they all originate in preëxisting cartilage. Alexander accepted the term ecchondroma as defined by Virchow and added four other groups of tumors: (1) Chondromas, true

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neoplasms invading the mother substance from which they originated and which in most cases are malignant; (2) mixed tumors, tumors made up of different tissues, *i. e.*, fibro-enchondromas, myxochondromas, chondrosarcomas, and chondromyxomas; (3) inflammatory—in this group but one case of questionable etiology was reported, and (4) general hypertrophy of one or all the cartilages of the larynx—three cases are noted in Alexander's statistics but none since.

It would seem that in the classification of cartilaginous tumors of the larynx the terminology should designate whether the tumor is benign or malignant. A chondromyxoma may be benign or malignant, but the name would not indicate this fact. A terminology indicating the combined microscopic and clinical conditions would be ideal, but until there is such a classification I shall accept that given by Alexander. The following is the report of a case of chondroma of the thyroid and cricoid cartilages:

P. E. O. (140068), male, aged forty-four years, a farmer, was examined September 1, 1915. He had had diphtheria thirty years previously and typhoid twenty-two years previously. There was no history of specific disease. He complained chiefly of having been hoarse for four years. When twenty-one years of age (twenty-three years previously) he was hit by a baseball on the right side of the neck, over the larynx. For a short time talking pained him, but he was never hoarse. Following a cold he noticed a lump on the outer side of his neck. This was never sore nor tender. One year previous to the present examination he consulted a physician, but nothing was done until six months later, when his home physician performed a tracheotomy on account of an attack of dyspnea. No other treatment was given. There was no loss of weight; no dysphagia. Although his voice was husky, he could make himself understood by plugging the tracheotomy tube with his finger.

Examination.—In the external examination of the neck a tumor was found, 1.5 by 1.5 inches in size, and extending to the right from the midline; its upper limit was one inch below the upper margin of the thyroid cartilage. It was rounded in outline, bony, hard, and fixed to the side of the larynx; the skin covering it was normal. The tracheotomy tube was in place. In examining the larynx the right cord, the false cord, and aryteno-epiglottic fold were found displaced toward the midline, a small slit being left for the passage of air. The tumor could be seen bulging on the right side of the larynx and covered by mucous membrane normal in appearance. The roentgen and general examinations were negative. The examination other than the laryngeal findings was negative. Diagnosis: Cartilaginous tumor of the larynx (Figs. 9 and 10).

On September 4, 1914, an operation was performed under novocain

anesthesia (E. S. J.).   An incision to the right of the midline exposed the

Fig. 9. -(140068.)   Chondroma of the larynx.   Right side of the midline of neck.

rounded hard tumor, which was found to have invaded the thyroid and cricoid cartilages and the upper part of the trachea.   Immediate microscopic examination of the tissue (frozen section) showed the growth to be a chondroma (Fig. 11).   The tumor could have been shelled out, but as this would have necessitated a large opening into the larynx and trachea, which would destroy the voice, it was thought best to leave a thin shell of the tumor and remove entirely the outer part, the more radical operation to be performed later should the condition recur. The wound was closed primarily with a small pack in the lower portion.   The convalescence was favorable and the patient was discharged about two weeks after the operation.   When he returned for examination April 6, 1916, there had been no change in the voice and no sign of the return of the tumor.   Externally, the neck was normal except for the scar and the tracheotomy tube.   The larynx was in the same condition as before the operation,   except that there was more room for the passage of air.
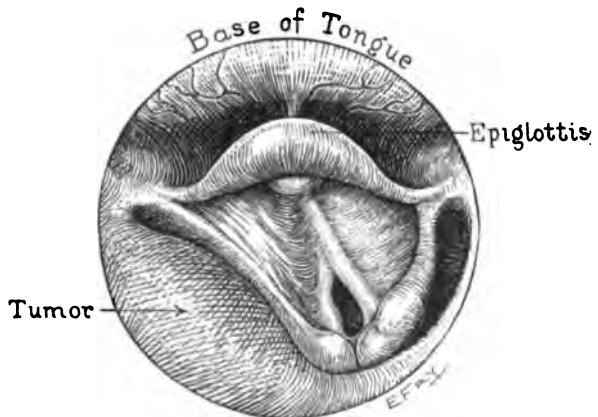
Fig 10. --Displacement of the right side of larynx.   Due to chondroma of the thyroid cartilage.

Etiology.— Nothing definite seems to be known regarding the etiology of these cartilaginous tumors.   Several hypotheses have been advanced, but none is borne out by the facts.   Bertoye has suggested

that the tumors are in some way associated with ossification of the cartilage of the larynx which begins during the fifth decade. Alexander, in his tabulation, cites the cases of 7 patients under forty years of age; Mansfeld cites 3 cases, and I have been able to collect 2, making 12 of a total of 47 in which the tumor was present in patients under forty years of age. This would not seem to substantiate Bertoye's theory. Eppinger thought that possibly the cartilage proliferation occurring about the joints at times might be analogous to cartilaginous tumors, but the fact that the tumors appear on the solid portion of the larynx, away from the
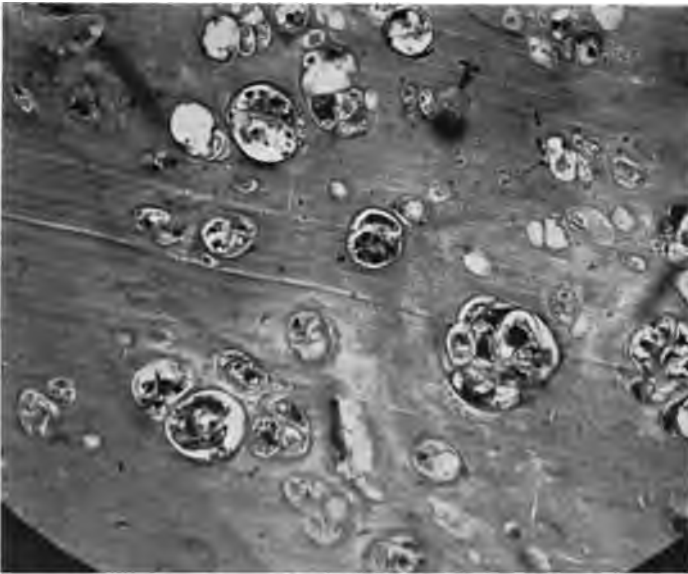
Fig. 11.—(140068.)   Cartilaginous tumor of the larynx (photomicrograph).

movable parts, does not verify this assumption. The question of chronic inflammation as a factor has been considered, but there are not sufficient data to establish such etiology.

My patient gave a history of injury of the side of the larynx by a blow from a ball nineteen years before the onset of hoarseness, but whether or not the injury was a factor in the etiology of the tumor is not known. However, this case seems to be the only one in the literature in which the etiologic factor of trauma might be considered. It is probable that until we discover the cause of tumors in general we shall not determine the etiology of cartilaginous tumors of the larynx.

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Symptomatology.—More than half of the cases found in the literature occurred in the fifth and sixth decades, although one case was reported of a girl seventeen years of age, and 5 cases that occurred in the seventh decade. Most of the patients were men; only 6 women have been noted. The symptomatology of these tumors is due to interference with the function of the larynx, either respiratory or vocal, and interference with swallowing. The symptoms are variable and depend on the location of the tumors, their size and their rate of growth. Hoarseness is usually an early symptom, but if the tumor is on the epiglottis or the arytenoid and does not interfere with the cords, this symptom will not be noticed. The same is true when the tumor is on the cricoid and entirely subglottic. Roos, in 1910, reported a case of subglottic tumor in which there were marked symptoms of dyspnea for five months, but no hoarseness. In the case of a tumor of the thyroid, hoarseness is usually an early symptom unless the tumor extends externally, in which case laryngeal symptoms are noted late.

Respiratory difficulty is dependent on the size of the tumor and the rate of the growth. Very large tumors may be present in the larynx, and the breathing space may be surprisingly small, but on account of the slowness of growth the symptoms of respiratory obstruction are not marked. A rapidly growing tumor causes pronounced symptoms. Cricoid tumors that usually spring from the posterior surface of the anterior part of the cartilage cause respiratory difficulties early, because of their location. Tumors involving the cricoid, as in Bolms' case and Moure's second case, may cause difficulty in swallowing if they extend toward the esophagus. Boerger's patient (Mansfeld's group) swallowed with difficulty for five years and was hoarse for a shorter period. Bolms' patient gave a history of an external tumor of the neck for one year, hoarseness for six months, and dysphagia for three months. With the larger tumors there is a sense of fullness and pressure, and in some instances the patient makes a heaving noise described as resembling the inspiratory spasm of whooping-cough. Three patients (those of Froriep, Türck, and Pretelle, reported by Alexander) died of dyspnea. Many patients have had to have emergency tracheotomies.

Locations of tumors.—In my group of nine cases (eight from the literature and one personal) the cricoid was involved in eight, the thyroid in two, and the arytenoid in one. As in Moure's and Daure's patient and in mine, the thyroid and cricoid were both involved; these patients are included in the eight cases of the cricoid group and the two

cases of the thyroid group.   In one of Garel's two cases the tumor was
probably an ecchondroma, but as this is questionable, I have designated
it as indeterminate.   The following table shows the cartilage involved
in my group of cases:

TABLE 1

Cricoid, 8
    Ecchondroma.. 1
    Chondromas... 5
    Indeterminate.. 1
    Mixed.. 1
Thyroid, 2
    Chondromas... 2
Arytenoid, 1
    Ecchondroma.. 1

The cartilages involved by the different types of tumors in Alex-
ander's, Mansfeld's, and the writer's cases were as follows:

TABLE 2

Cricoid, 24
    Ecchondromas.. 7
    Chondromas.. 11
    Mixed tumors.. 5
    Indeterminate... 1
Thyroid, 14
    Ecchondromas.. 5
    Chondromas.. 7
    Mixed tumors.. 2
Arytenoid, 4
    Ecchondromas.. 4
Epiglottis, 3
    Ecchondromas.. 3

It will be seen from the table that the arytenoids and epiglottis are
attacked by ecchondromas only, while the cricoid and thyroid cartilages
may be involved by any of the types of tumors.   The cricoid is involved
nearly twice as frequently as the thyroid.   Chondromas or mixed
tumors do not involve the arytenoids or the epiglottis.

Objective findings.—The normal appearance of the mucous membrane,
not alone surrounding the tumor, but in the entire larynx, and the absence
of signs of congestion, unless some temporary acute infection is present,
are characteristic in cases of cartilaginous tumors.   The hardness felt
when touching the tumor with a probe is different from that of any other
type of laryngeal tumor, although in some cases, as in the case reported
by Roos, the tumor is somewhat soft.   Cartilaginous tumors of the
larynx arise from one of the cartilages of the larynx, so that the location
of a tumor may be of value also in differentiating it from other types.

An external tumor of the neck fixed to the larynx, very hard, without signs of inflammation, would suggest a cartilaginous tumor. In some cases the roentgen ray shows a shadow which is of value in making the diagnosis. The question of malignancy in these cases is usually ruled out without difficulty, but must be considered. The absence of glandular enlargement is a characteristic feature, although this point in itself is of little value, since other benign tumors have no glandular enlargement and even epitheliomas may exist for years without metastasis. Fränkel in 1893 reported a case in which, six months following a radical operation for chondroma of the cartilage, two glandular swellings developed in the neck. These were removed, and on examination proved to be "slimy, softened chondromatous glands." This is the only case reported in which a cartilaginous tumor of the larynx developed metastasis.

Cartilaginous tumors of the larynx vary in size from that of a small tumor on the arytenoid to that of a tumor involving the thyroid and cricoid cartilages and also the upper rings of the trachea. The ecchondromas are usually the small tumors; the chondromas and mixed tumors, as a rule, grow to a much larger size. The ecchondromas grow slowly, while the chondromas are usually more rapid in development. The only safe way to make an absolute diagnosis is to remove tissue for microscopic examination.

Histopathology.—Detailed descriptions of the microscopic pathology of cartilaginous tumors of the larynx are not frequent in the literature. The ecchondromas are the same in structure as the cartilage of the larynx, consisting of hyaline cartilage. Sometimes ossification is seen.

In referring to chondromas, Alexander states that there is an irregularity in the size and shape and arrangement of the cells, and that the cartilaginous tissue shows an unusual energy of growth. In the older tumors, cyst formation may occur from a retrogressive change in the tumor. Calcification may also be seen. The mixed tumors present pictures too varied to permit a review of their microscopic appearance. In regard to the histology of inflammatory tumors and the general hypertrophy group, nothing is noted in the literature.

Treatment and prognosis.—Small ecchondromas may be removed by the endoscope and this seems the method of choice, although in some instances it is necessary to do a thyrotomy. The chondroma and mixed tumors present a more difficult problem. In almost all cases of the latter there is some dyspnea. Three patients of Alexander's group died of

suffocation before tracheotomy could be done. In considering the operative treatment of these patients, it must be remembered that the voice should be preserved as long as possible. If the tumor is not malignant and its removal would destroy the voice, some conservative treatment is indicated. The end results of cases in which a radical operation has been done further impress this feature. However, if the tumor is malignant, the most radical operation should be done.

End results in 22 cases of chondromas and mixed tumors (Alexander's, Mansfeld's, and the writer's statistics).—Three patients choked to death without tracheotomy; one died following tracheotomy. Fifteen had external operations varying from complete laryngectomy to thyrotomy and partial or complete removal of the tumor. One patient had roentgen treatment and is reported "better"; one had repeated endolaryngeal operations with "good results"; one was not operated on and the subsequent history is not known. Of the 15 patients operated on, 5 died from pulmonary complications shortly after operation and 5 improved for varying periods of time the length of which was not stated. One patient was doing well seven and one-half months after operation; the condition of two others was good after the operation, but the end results are not stated. In one the condition "relapsed," and in the case of another the tumor was incompletely removed and the results are not stated.

REFERENCES

1. Alexander, A.: Die Knorpelgeschwülste des Kehlkopfes (Eschondroses, Exostosen, Ecchondrome, Chondrome, Enchondrome). Archiv f. Laryngol. u. Rhinol., 1900, x, 181–254.
2. Bertoye, H.: Quoted by Alexander, A.: loc. cit., 196.
3. Boerger: Quoted by Mansfeld, D.: loc. cit., 514.
4. Bolms, J.: Ueber zwei Fälle von Chondrom am Ringknorpel. (Bonn) Salzwedel, 1912, A. Menzel, 32 p.
5. Bruns, P.: Enchondrom des Kehlkopfs. Beitr. z. klin. Chir., 1887, iii, 347–353.
6. Eppinger, H.: Patholog. Anatomie des Larynx und der Trachea. In: Klebs' Handb. d. pathol. Anatomie. vii, Berlin, 1880, p. 236.
7. Fränkel, B.: Demonstration eines Chondroms des Larynx. Berl. klin. Wchnschr., 1904, xli, 400.
8. Froriep, R.: Pathol. anat. Abbildungen aus der Sammlung der Königl. Charité. Heilanstalt zu Berlin. Weimar, 1836.
9. Garel, J.: Fibrome kystique volumineux du larynx; extirpation endolaryngee sans tracheotomie. Ann. d. mal. de l'oreille, du larynx, etc., 1891, xvii, 107–110.
10. Mansfeld, D.: Ueber Knorpelgeschwülste des Kehlkopfs nebst Mitteilung eines Falles von Chondroma myxomatodes. Arch. f. Laryngol. u. Rhinol., 1909, xxii, 508–523.
11. Moure, E. J.: Des enchondromes du larynx. Rev. hebd. de laryngol., 1910, xxx, 48–61.
12. Pretelle, F.: Quoted by Alexander, A.: loc. cit., 199.
13. Roos: Myxochondroma laryngis subglotticum. Ztschr. f. Ohrenh., Wiesb., 1910, lxii, 228–230.
14. Türck, L.: Klinik der Krankheiten des Kehlkopfes und der Luftrohre. Wien, 1866, 317–321. Mit einem Atlas. Taf. xi.
15. Virchow, R.: Die krankhaften Geschwülste. Berl., Hirschwald, 1863–1867, i, 442.

TABLE 3

Case No.	Author	Sex	Age	Subjective History	Objective Findings	Operation	Location of Tumor	Pathologic Diagnosis	End Results
1	Garel, J.	F	35	Patient came for throat trouble, vocal and respiratory.	Below the left vocal cord was a tumor with its convexity extending to the midline of the trachea. The tumor was hard and resisted the probe.	Thyrotomy. Tumor operated upon.	Cricoid cartilage.	Enchondroma.	Several days after operation pulmonary complication caused death.
2	Durand and Garel, J.: Les chondromes du cartilage cricoïde. Ann. d. mal. de l'oreille, du larynx, 1908, xxxiv, 629-54.	M	57	Ten months' history. Began by dyspnea on exertion, increasing in intensity and frequency. Voice not a good tone. Breathing on exertion resembled the respiratory spasm of whooping-cough.	Laryngeal examination showed a round, regular hard tumor in the subglottic region under the left vocal cord, covered by normal mucous membrane. Patient refused operation at this time but submitted to it 7 mos. later when dyspnea became marked.	Low tracheotomy was done; operation 1 month later. Incision extended through the thyroid, cricoid, and first two rings of trachea. Tumor the size of a nut was seen on the posterior wall of cricoid. The tumor was curetted off and the wound closed.	Cricoid.	Enchondroma.	No recurrence.
3	Landwehrmann: Enchondrose am Giessbeckenknorpel. Ztschr. f. Ohrenh., 1909, lix, 380.	F	28	Hoarseness for two years.	Nodular growth on the right vocal process, under the origin of the right true cord. Firm growth, a few millimeters in length and width. During phonation it moved to the opposite side.	Removed with double curet.	Arytenoid.	Cartilaginous tumor.	Eight weeks after removal of tumor voice not clear because of partial adduction paralysis.
4	Moure, E. J., and Daure: Enchondrome volumineux du larynx. J. de Méd. de Bordeaux, 1910, xl, 43.	M	52	Six years ago noticed difficulty in speaking and weakening of the normal timbre of his voice. Laryngeal examination showed a tumor on the left side of the larynx the size of a nut. Functional disturbances continued more marked. Hoarseness and dysphagia for two and one-half years. Dyspnea at times for two years. General health good.	Tumor hard, globular, and fixed on the external left side of the larynx, extending down to the trachea and displacing the larynx to the right. Gland in carotid region on the left side; hard, movable. Laryngeal examination showed on the level of the left aryteno-epiglottic fold a smooth round tumor the size of a mandarin orange and concealing a large part of the laryngeal cavity. Mucous membrane normal except for dilated vessels. Radioscopic examination showed a shadow in the region of the thyroid cartilage which exceeded the limits of the cartilage and extended down over the trachea.	Preliminary tracheotomy under cocain. Three weeks later operation under cocain. A thyrotomy was done in the midline, exposing a multilobular round tumor which had invaded the inferior part of the larynx and also the pyriform sinus. The neoplasm was adherent to the posterior surface of the cricoid cartilage.	Thyroid and cricoid.	Benign chondroma.	Not stated.

No.	Reference	Sex	Age	History	Findings	Operation	Part involved	Diagnosis	Result
5	Moore, K. J.: Des enchondromes du larynx. Rev. hebd. de laryngol. 1910, xxx, 48-61.	M	38	For one year increased respiratory difficulty which was thought to be cardiopulmonary. For two and one-half weeks before: had been worse. One severe attack of dyspnea.	Marked dyspnea. Voice husky. In subglottic region on deep inspiration multilobular tumor could be seen mostly on the right side of the trachea; not palpable externally.	Tracheotomy under cocaine. Operation under cocaine. Upper five rings of trachea incised. The tumor, mostly on the left side, bulging the trachea and forming a diverticulum, was removed in pieces and by curet. Growth was the size of a chestnut.	Thyroid, cricoid, and trachea.	Fibrochondroma.	Acute myocarditis one week after operation. Died. Necropsy: tumor much more extensive than was thought. Cricoid cartilage entirely deformed and friable. Lumen of cricoid small. Tumor extended into submucous layer of esophagus and down to sixth ring of trachea. Operation removed portion of tumor that projected into trachea.
6	Roos: Myxochondroma laryngis subglotticum. Ztschr. f. Ohrenh. 1910, lxii, 428-30.	M	44	Dyspnea on slight exertion noticed four or five months before; became progressively worse. Much trouble when lying down. No cough, no dysphagia, no hoarseness.	Slight respiratory stridor at rest; more marked on exertion. General examination negative. Externally nothing palpable in the neck. No sinuses. Throat negative. Voice clear. Larynx normal. Cord normal in function. Tumor visible below the cord on posterior portion of the right wall covered by normal mucous membrane. Small slit posteriorly and to the left for the passage of air.	Ether-morphin anesthesia. Midline incision. No previous tracheotomy. Upper rings of the trachea, the cricoid, and the lower half of the thyroid cartilage divided. A soft tumor the size of a cherry arising from the upper and posterior part of the cricoid cartilage exposed. Its base was the size of a coffee-bean. The tumor was excised and curetted, the base cauterized, and the wound closed primarily.	Cricoid.	Hemorrhagic myxochondroma (benign).	Seven and a quarter months after operation the larynx was normal. No recurrence.
7	Bolms, J.: Über zwei Fälle von Chondrom am Ringknorpel. Bonn, Menzel, 1912, 32 p.	M	66	One year before, following influenza, patient noticed swelling of the throat. A tumor enlarged slowly until the size of a fist. Six months later hoarseness developed. Some dysphagia for three mos. When examined, some dyspnea on exertion. No weight loss.	Firm, nodular, fixed tumor, definitely circumscribed over the left jugular vessels and extending above the upper limits of the larynx. No glandular enlargement. Displacement of the larynx to the right. Immobility of the left vocal cord. Mucous membrane of the larynx normal. No localized tumor formation visible. Roentgen ray showed a bowing of the trachea to the right.	Operation under ether: curved incision over the highest portion of the tumor. Tumor fixed to the cricoid cartilage; also to the trachea, but not to the thyroid, was removed. Tumor had entirely destroyed a portion of the cricoid cartilage and the upper three rings of the trachea had been involved.	Cricoid cartilage.	Chondroma.	Not stated.
8	Salomonsen, K.: (Clinical contribution on enchondroma of the larynx.) Hosp. Tid. 1914, 5 R, vii, 963-72.	M	56	Six months' hoarseness and dyspnea on exertion. No dysphagia. Hoarseness and dyspnea increasing.	Laryngeal examination shows the glottis askew from the right side in front to the left side posteriorly. In the subglottic region underneath the right vocal cord was seen a round growth the size of a cherry with a broad base. The vocal cords were normal. No ulceration.	Ether anesthesia. Low tracheotomy incision extended up through the trachea and cartilage. A tumor the size of a walnut visible in the right subglottic region was curetted out. Wound completely closed.	Cricoid cartilage.	Cartilaginous tumor.	Tumor incompletely removed.

AN EPIDEMIC OF SEPTIC SORE THROAT DUE TO MILK*

E. C. ROSENOW AND C. L. v. HESS

During the early part of March there occurred in Galesville, Wis., a town of about 1200 inhabitants, a sudden outbreak of severe sore throat. The symptoms were so severe, and the outbreak was so sudden, that the authorities and physicians became alarmed.

March 12 one of us was urged to investigate the epidemic. The symptoms were strikingly like those in the milk-borne epidemic of septic sore throat which occurred in Chicago during the winter of 1911–1912, studied by Capps and Miller, and Davis and Rosenow. The relation of the cases to the milk supply was suspected, and pasteurization or boiling of the milk was advised pending the investigation. March 15 it had become apparent that the cases occurred chiefly in families who used milk from a certain dairy. Inspection of the throat and microscopic examination of a smear from the tonsils in the first case recalled at once the picture that was observed in the Chicago epidemic, namely, the presence of much mucus, diffuse redness of the throat, and enormous numbers of diplococci in smears. The subsequent examination from house to house of some thirty patients showed clearly that this was not an epidemic of ordinary tonsillitis, so prevalent at this season of the year, but one presenting the typical picture of "septic sore throat." In some households all members of the family were stricken, from grandparent to child, each being too sick to care for the others.

After an incubation period of from one to three days the attack usually began with a severe chill or by several less severe rigors. This was usually followed by restlessness, high fever, ranging from 102 to 105 F., intense aching of the muscles, extreme prostration, great pain on swallowing, and tenderness on one or both sides of the neck due to enlarged lymph-glands and to the accompanying edema and infiltration. At first the amount of inflammation of the throat was slight, considering

the severity of the constitutional symptoms.   Later, in the severe cases, intense diffuse hyperemia and edema of the pharynx, tonsils, and soft palate supervened.   Small superficial ulcers were common on the uvula and pillars.   There was temporary edema of lips and eyelids.   The pulse was relatively slow.   The lips and finger-nails were blue.   The acute symptoms lasted usually from three to five days, but in some the fever became septic in type as the enlargement of glands and infiltration in the neck persisted for some weeks.   Relapses and complications were common.   They occurred usually after the first week or ten days of illness. Erysipelas of the face and otitis media were the most frequent complications observed.   Pleurisy, pericarditis, endocarditis, arthritis, peritonitis, myositis, and synovitis were noted.   Symptoms simulating acute rheumatic arthritis, one of the complications, were found in most instances to be due to myositis and tenosynovitis.   Pneumonia and nephritis were not observed.

About 200 persons were affected, of which approximately 95 per cent consumed the contaminated milk.   In some instances the drinking of a single glass of the infected milk was followed within forty-eight hours by typical attacks.*   There have been eleven deaths, due chiefly to erysipelas, peritonitis, or cardiac complications.   Promptly after the milk was boiled the spread of the epidemic ceased.   The few "secondary" cases which developed were less severe, and complications and relapses were noticeably less common after the milk was boiled.   Persons who had had their tonsils removed previously developed mild symptoms or none at all.

Swabs were made jointly with Dr. Thompson from six patients and cultures from the blood in one.

At the dairy it was learned, first, that during the three weeks previously all of the milkers and the wife of one of the dairymen either had been or were still ill with severe sore throat; second, that the milk from well-kept, clean Jersey cows was strained into 10-gallon cans and then bottled from a 5-gallon bottler; third, that a number of cows had had mastitis for some weeks, but this condition was no more prevalent this winter than other winters; and fourth, that the milk from infected quarters of the udders was discarded.   The milk from three cows (Cows 1, 2, and 3) having mastitis was collected jointly with Drs. Thompson

and Henika, of the State Board of Health.*   This was done by discarding
the first strippings and then milking the contents into sterile bottles.
In one cow (Cow 1), the right hind quarter of the udder was infiltrated
and tender.   The material obtained (60 c.c.) looked more like pus than
milk.   The other quarters were normal, but 90 c.c. of milk were taken
from the anterior quarter of the same side for control tests.   Smears of
the material from the quarter showing mastitis showed an enormous
number of gram-positive diplococci (some of which showed capsules),
single and in short chains, and many leukocytes.   Blood (human) agar
plates inoculated with a loopful of this material showed in twelve hours
countless numbers of grayish, translucent, moist, spreading colonies
surrounded by a rather wide but somewhat hazy zone of hemolysis.
Smears from the centrifugalized sediment of the control milk from Cow 1
showed four colonies of the same streptococcus and no other bacteria.
Dextrose broth cultures showed marked diffuse turbidity due to diplo-
cocci which were single and in short chains.   These plated on blood agar
yielded the same streptococcus in pure form.

Smears and cultures from the mastitis milk from Cow 3 showed
exactly the same streptococcus, while the material from the infected
quarter of Cow 2 showed staphylococci and a few grayish colonies of
streptococci but not the hemolyzing streptococcus.

Smears from the swabs of the throats of five patients showed many
diplococci and leukocytes.   The cultures on blood-agar plates yielded
large numbers of colonies of streptococci exactly like those from the in-
fected milk.   On some of the agar plates were a few green colonies of
streptococci, staphylococci, colon bacilli, and Micrococcus catarrhalis.
The preponderance of the characteristic streptococcus on these plates
was a striking picture.   The colonies like those found in the Chicago
epidemic when first isolated differed from the usual hemolytic strepto-
coccus in that they were larger, less opaque, and more moist, and the
hemolysis was less marked and less sharply defined.   After cultivation
for a short time, in some instances in the third culture generation, these
peculiar features had disappeared simultaneously with the capsule and the
colonies were indistinguishable from the usual hemolytic streptococcus.
One of the six patients failed to show the hemolyzing streptococcus.
The fermentative reactions of the streptococcus from the milk and

* On arrival at the dairy, Dr. Henika reported the finding of numerous "streptococci"
in the centrifugalized sediment of a sample of the contaminated milk procured in the open
market.

throats were identical.   Dextrose, lactose, saccharose, and salicin were attacked; raffinose, mannite, and inulin were not.

Animal Experiments

The virulence of the streptococcus, the missing link in the chain of evidence to prove the milk guilty, was demonstrated the next day, March 16, and was so reported to the Galesville authorities.   The following protocols suffice to illustrate:

Rabbit 1172.—A medium-sized white rabbit was injected intra-peritoneally, March 15, at 11.45 P. M., with 3 c.c. of the pus-like material from the mastitis quarter of Cow 1.

March 16, 7.30 A. M.: The rabbit was extremely ill; unable to stand. At 11.30 A. M. it was found dead.   The peritoneum appeared opaque and dry.   There was no free fluid.   There were marked degeneration of the liver and myocardium and cloudy swelling of the kidney.   The joints, stomach, spleen, and lungs showed no changes.   Smears from the peritoneum and blood showed many gram-positive diplococci, single and in short chains.

March 17: The blood-agar cultures of the blood showed large numbers of colonies of the streptococcus injected.   Dextrose broth cultures showed diffuse turbidity and smears showed diplococci, single and in short chains.

Rabbit 1174.—A medium-sized gray rabbit was injected intra-peritoneally, March 15, 11.50 P. M., with 1 c.c. of the salt-solution suspension of the swabs from six patients.

March 16, 7.30 A. M.: The rabbit was very ill.   At 10.30 A. M. it was found dead.   The peritoneum was dry and opaque.   There was marked cloudy swelling of the myocardium, kidneys, and liver.   Smears from the peritoneum showed very many gram-positive diplococci and few leukocytes showing little phagocytosis.   Smears from the blood showed a moderate number of gram-positive diplococci in short chains.

March 17: Cultures from the blood on blood-agar plates showed large numbers of colonies of the streptococcus injected.   Dextrose broth cultures showed marked turbidity, and in smears diplococci, single and in short chains.

Two white mice (Mice 44 and 45), injected at the same time, one subcutaneously with 0.3 c.c. of the mastitis material, the other intraperitoneally with 0.1 c.c. of the salt-solution suspension of the throat swabs, were ill the next day and died from streptococcemia, March 17.

A mouse (Mouse 46), injected intraperitoneally with 2 c.c. of the sediment of the mastitis material from Cow 2, in which the blood-agar plate cultures failed to show the streptococcus, died March 17.   There was a dry peritonitis and there were a large number of the typical streptococci in the blood.

The effect of heating the mastitis material from Cow 1 to 60 C. (140 F.) was determined. Cultures made just prior to heating showed countless numbers of the typical streptococcus, while after pasteurization the cultures were sterile. The unheated material was injected as follows: 2 c.c. subcutaneously into one large rabbit, 3 c.c. intraperitoneally into another rabbit, and 0.5 c.c. intraperitoneally into a mouse. The rabbit injected subcutaneously and the mouse died within forty-eight hours from streptococcemia. The former showed marked subcutaneous edema at the point of injection, acute regional lymphadenitis, acute pericarditis, and edema of the lungs. The mouse showed peritonitis. The rabbit injected intraperitoneally became ill but ultimately recovered. The animals injected with corresponding amounts of the pasteurized material remained well.

Similar experiments were done with a sample of milk obtained in Rochester; cultures of which showed large numbers of non-hemolyzing streptococci and a moderate number of colon bacilli. Animals were injected as above, first, with this milk as obtained and kept at room temperature for twenty-four hours; second, with the milk inoculated with the virulent streptococcus (Cow 1) and kept at room temperature for twenty-four hours, and third, with the latter after pasteurization. Those injected with the uninoculated milk remained well, as did those injected with the pasteurized material, while those injected with the milk inoculated with the virulent streptococcus either died or became ill.

It has been held by some that to determine the virulence of streptococci by injection is not sufficient to prove the etiologic relationship in these and similar studies. We therefore instituted experiments in which the methods of inoculation simulated those occurring in the epidemic; that is, we fed the infected material and swabbed the throats and scratched the skin. In swabbing the throats, care was exercised to avoid injuring the mucous membrane.

Two mice (Mice 47 and 48), whose throats were swabbed once and which were fed bread soaked in the infected material, died in six and three days, respectively. The latter developed swelling of the left side of the face resembling erysipelas. The former had no evidence of infection of the throat, but showed edema and hemorrhagic infiltration of the visceral pericardium covering a large part of the left ventricle, acute splenitis, and approximately 500 and 1200 colonies of the typical streptococcus in a drop of blood and pericardial fluid, respectively.

Two mice (Mice 49 and 50) were fed bread soaked in the infected material. Mouse 49 has remained well. Mouse 50 died in six days and showed several small epicardial hemorrhages, acute splenitis, and edema

of the tissues surrounding the throat, but no apparent enlargement of the lymph-glands and no inflammation of the mucous membrane of the throat. The blood showed countless numbers of the typical hemolyzing streptococcus.

The results in a monkey (Monkey 120) are given in detail. March 18 the throat was swabbed with mastitis material from Cow 1, and the skin on the left side of the nose scratched with a wire dipped in the same material. Bread soaked with the material was placed in the cage, no other food being given for one day.

March 19, 10 A. M.: The left side of the face surrounding the scratch

Fig. 12.—Monkey showing erysipelas of the face.

was swollen and red, including the lower eyelid. There was no discharge from the nose and no perceptible swelling or redness of the throat. At 5 P. M. the swelling of the left side of the face was more marked and the temperature was 103 F. The throat was again swabbed.

March 20: The swelling of the face was more marked, the left eye was swollen nearly shut, and the edema extended to within 2 cm. of the ear. The right side of the face showed no involvement.

March 21: The swelling of the left side of the face had subsided perceptibly; the skin was wrinkled and beginning to desquamate; there was marked swelling of the right side of the face, as shown in the ac-

companying illustration; the temperature was 103 F.; the affected area was hot and red.

March 23: The animal's face was still much swollen and red; the monkey seemed ill; the temperature was 103.5 F.

March 24: The swelling of the left side of the face had markedly subsided.

March 25, 10 A. M.: The swelling of the face was more marked, especially on the right side; the right eye was nearly closed; the animal appeared ill; the temperature was 103 F. At 12 noon it was found dead. There were marked swelling and edema of the whole face, extending to the ears on both sides, well into the neck, and over a large portion of the scalp. The submaxillary lymph-glands were enlarged and edematous. In the pharynx was a small amount of pus. The tonsils were not perceptibly enlarged, but the adjacent lymph-glands and surrounding tissues were edematous and hemorrhagic. A small amount of slightly blood-tinged fluid was found in both middle ears. The mucous membrane of the nares was normal, but that in the pharynx, including that surrounding the eustachian tubes, was hyperemic and covered with much mucus. In the peritoneal and pericardial cavities was a large amount of slightly turbid fluid containing hemolyzed blood, leukocytes, and many streptococci. The epicardium was moist and edematous, particularly along the blood-vessels and at the base. The anterior leaflet of the mitral valve was edematous at the base, and near the periphery were two small hemorrhages. There was hemorrhagic edema along the base of the pulmonary and aortic valves. The middle aortic semilunar cusp contained a large edematous nodule along the line of closure. The myocardium, kidneys, and liver showed cloudy swelling. The left infrapatellar bursa was hemorrhagic and edematous. There were no other lesions. The blood was markedly hemolyzed.

March 26: Blood-agar plates from the subcutaneous fluid, the peritoneal fluid, the pericardial fluid, and the blood showed the typical streptococcus in large numbers in pure form. The exudate from the middle ears showed chiefly green-producing streptococci resembling pneumococci and a few colonies of the typical streptococcus.

SUMMARY AND CONCLUSIONS

The clinical picture in this epidemic was typical of "septic sore throat" as described in numerous other milk-borne epidemics. Etiologic relationship of the streptococcus found in the milk was proved. The disease occurred almost exclusively in persons who consumed the milk. In some instances the drinking of one glass was sufficient to bring on an attack. The streptococcus was found in enormous numbers in the material from mastitis quarters of the cows' udders and in small numbers in a normal quarter. It was also isolated in large numbers from the

throats of patients. High virulence of the streptococcus was proved by inoculation of animals. The lesions produced resembled those found in patients, especially in those animals which in the methods of inoculation simulated those which occurred in the epidemic. Erysipelas was produced in a monkey by scratching the skin with a wire dipped in the infected material. In the same monkey inflammation of the throat associated with acute enlargement of the lymph-glands in the neck, with surrounding edema and otitis media, followed swabbing the throat with cotton saturated with the same material. Peritonitis, pericarditis, endocarditis, myocarditis, and synovitis were common in the animals as in patients. Heating the milk to 60° for twenty minutes was sufficient to render it innocuous.

Virulent bacteria may be present in the udder of cows with no demonstrable sign of disease. It is practically impossible to handle milk without risk of contamination from human and other sources, even though the rigid technic of an operating room be employed. Since milk is such an excellent culture-medium, inspection of dairies, certification and grading of milk according to sediment tests, and bacterial counts as now practised, while valuable, cannot permanently safeguard the public health. Efficient pasteurization should be universally adopted.

PEPTIC ULCER AND GALLSTONES IN UPPER ABDOMINAL DIAGNOSIS*

C. GRAHAM

The stomach is a center around which a multitude of functional and pathologic symptoms revolve. The pathologic conditions which cause the gastric disorder may be due to various lesions, either local, focal, or reflex, or they may be due to general infections. Physiologic and pathologic laboratories have done and are doing a great work in clearing up problems in diagnosis. Surgery has been illuminating by dealing at first hand with the pathologic lesions. Roentgenology has given a wonderful impetus to general diagnosis, and in no realm has its influence been more commanding than in the gastric region. Despite all these generous advances, the difficulties that surround upper abdominal diagnosis are so great and varying that interest in its development continues—really grows.

The physician who would reach a modest degree of proficiency in diagnosis must be able and willing to work without wearying. He must acquire proficiency through the experience, gained first hand in directed work at our great laboratories, hospitals, and clinics. It is less often attained by the clinician who directly leaves his medical college to meet single-handed the pathology of the world.

Again, the clinician must needs have the proper diagnostic attitude. He must listen cheerfully and willingly to the patient's story. The patient may be so acute in his observations as to bring a diagnosis clearly and without travail to you; therefore harken carefully and modestly to what his attending physician has perceived and told. Do not bristle or oppose, and do not attempt to prove the physician inconsistent and incorrect. The observations of the clinician who has attended the patient through an attack have significance and should be wisely weighed. Of course, one should not be easily misled and make a

diagnosis on another man's observations unless his own mind reaches the same conclusion frankly. Be searching, cheerful, and receptive, an attitude which will find a reward.

A working knowledge of surgical anatomy, and this kept clearly in mind when developing a history, carries one a great way toward correct conclusions. To be sure, a proper seasoning of judgment, a moderate, well-directed experience, coupled with an intense willingness to work, are needed.

Another requisite for diagnostic aptness is the ability to think in pathologic multiples. He who can clearly keep in mind the multiplicity of pathologic conditions, and group the symptoms as expressed in complaints of the stomach, will most often reach accurate results. When interpreting upper abdominal pain, we find a multitude of causes. If we hold in mind only gastric lesions, we may miss the gallbladder, the pancreas, and the kidney. Cardiospasm, duodenal lesions, anginas, and appendicitis are called "stomach" by the patient. Tuberculosis, cardiorenal disease, syphilis, brain and cord tumors, meningeal irritation, and a hundred and one other conditions are all often translated by the patient as stomach trouble and he seeks help for the stomach only. This leads us to consider the value of good history taking. No methods or measures are of more importance to sound and exact diagnosis than the carefully developed history with the proper interpretation and logical correlation of symptoms. The history need not be profuse, but it should cover the facts of inheritance, occupation, accidents, previous diseases, operations, etc. It should carefully include comprehensive details of the symptoms from which the patient seeks relief—when they were first experienced, how shown, where located, and what their relation. Also should be noted the time of onset of symptoms, the development of each, which took precedence, their change in order and severity during the time of trouble, and intermissions or remissions should be recorded. Compare the early and late symptoms if they have been prolonged. These details, simply and precisely carried out, coupled with a careful and complete physical examination, leave less to be done by the laboratories, are better form, and bring diagnosis nearer to a scientific basis. Further and very important—no clinical history is complete, and its value is greatly to be questioned, which does not have the stamp of the frank diagnosis of the physician who writes it and who made the physical examination. The clinician should endeavor to leave to surgery, to the laboratories, and to the roentgen ray, the stamp of approval only.

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Ulcer.—In the diagnosis of peptic ulcer let us consider first what the chances are of locating the lesions from the history given by the patient and gathered and correlated by the clinician. We find in our series of histories no symptom or group of symptoms that always warrant ulcer location. If we call all peptic ulcers duodenal ulcers, then we may say our percentage of correct diagnoses is about 75, because 75 per cent of peptic ulcers are duodenal. Such a standard would be scarcely honest—certainly not interesting. What we term a rather typically duodenal history gives us about 75 per cent correct localizing diagnoses: the other 25 per cent drops into what we deem the gastric syndrome. In our histories of gastric ulcer about 25 per cent are of the typically duodenal type, thus leaving 75 per cent to fall into the gastric type. The histories, then, of one-fourth of our gastric ulcers are as clearly of the duodenal type as are many of the duodenal themselves, and just as clearly are one-fourth of the histories of the duodenal of gastric type. So the clinician who depends solely on the history for ulcer location will often find himself wrong. Neither does pain as to kind, location, or severity point clearly. The time of pain or control gives us clear points but not positive evidence. We feel that these varying symptoms do help to a considerable degree, that they are often important indications as to location, but they are only helps—at times they are a good working rule, but by no means a law.

The clinical diagnoses in a series of 2919 histories of duodenal and gastric ulcer patients (duodenal 2223; gastric 696) who came to operation are given here to show our difficulties in locating lesions from a study of clinical histories.

In 64.3 per cent of the cases a primary diagnosis of duodenal ulcer was made, while 16.5 per cent were put down as gastric ulcer. In about 273 cases (12.2 per cent) gallstones entered largely into the diagnosis. Of these 273, 91 (4.1 per cent) of the patients were sent to operation without test-meal or roentgen ray and with no other diagnosis mentioned. At operation many of these patients proved to have the chronic perforating type of ulcer, though others showed only adhesions to the gallbladder.

In 108 (4.9 per cent) of these 2223 duodenal ulcer cases, appendicitis figured in the diagnosis, while cancer was considered in but 1 per cent. This leaves about 0.7 per cent unclassified.

Of the 696 gastric ulcers that came to operation, 438 (62.9 per cent) were classified as gastric, 161 (23.2 per cent) duodenal, and in 34 (4.8 per

cent) the gastric diagnosis was placed in second position. The gall-bladder was primarily considered as the chief offender in 45 cases (6.4 per cent), and in half of these it was the only diagnosis given.

Cancer was considered in 4.3 per cent of the cases, appendicitis in 1.1 per cent, and the unclassified amounted to about 1.7 per cent. If pain, the chief symptom, is considered alone, and the time of its appearance is the guiding factor, we find that in 50 per cent of gastric ulcers there is pain beginning from two to five hours after meals, and in the other 50 per cent, before two hours. In duodenal ulcer there is pain in 75 per cent, beginning from two to five hours after eating, and in the remaining 25 per cent, before two hours.

Points That May Aid in a Clinical Differentiation of Gastric and Duodenal Ulcer.—Duodenal histories have a longer course in years (11 per cent) than do gastric, perhaps in part because there is less chance of latency when they are situated in the duodenal area. The longer the history, the more likely is the ulcer to be duodenal. The higher the acid, the lower the ulcer. Hemorrhage is oftener present in gastric ulcer. More duodenal ulcers than gastric ulcers are diagnosed as gallbladder trouble. Position (reclining) and pressure-ease are more indicative of gastric than of duodenal ulcer. Night pain is more frequent in duodenal ulcer. Ease before the next meal occurs more often in gastric ulcer. The higher ulcers seem to run shorter attacks, are repeated oftener, or with only remissions; so they run month by month, the pain earlier, without that constant decided food and soda ease, and symptoms varying with the amount and kind of food. So, too, in high ulcers, small amounts and bland food may give ease, while larger amounts or heavy food disturb and give immediate pain. In low ulcer the large meal offers more chance of ease. With the high ulcers there is oftener regurgitation of burning hot water, sour hot water, or a salty liquid running from the mouth, than with duodenal ulcers. Bloating and pressure occur more frequently in gastric ulcer. High-ulcer pain is farther up and more to the left. Coarse foods and large amounts of food are more apt to cause distress in gastric than in duodenal ulcers and more in large ulcers than in small. Deeply undermined duodenal ulcers are often much like high ulcers of large area. Continuous symptoms are four times more common in gastric than in duodenal ulcer. The size of the ulcer seems to have quite as much or more influence on symptoms than has the position. Small ulcers with high location often give clear-cut duodenal ulcer history. Large ulcers wherever situated give shorter

food ease; they tend to constant symptoms; more remissions than in-termissions; food is more apt to give immediate distress, and the patient is easier with the stomach empty. These ulcers lose type.

To the history taker the difficulties of ulcer location are great. In-deed, he hesitates and should hesitate, because there is little reason to believe that pyloric ulcers vary much in symptoms from the symptoms due to ulcer in the duodenum. The symptom variations do point to ulcer location, but they give no hard and fast lines. Hence we feel that the physician who can locate all or most peptic ulcers by clinical symp-toms only has developed much more accuracy than we have attained. The roentgen ray does locate the disease whenever its findings are posi-tive; therefore its influence is striking and it has the exactness that the clinical histories lack. But the x-ray has its difficulties, and we need all our combined forces to make a respectable showing. We see no great benefit to the patient in such exact localization so long as the peptic lesion is diagnosed and the patient gets proper medical or surgical atten-tion. Only it is a comforting sort of feeling, when later the x-ray or surgery proves the accuracy of one's observations.

Symptomatology.—In the majority of instances the early history of peptic ulcer is clear-cut and definite, and is typically given, by the pa-tient in the twenties. There are attacks of pain, pressure, burning, or a strange nervous weakness that comes from three to five hours after meals. Most often in the early period this pain, distress, or weakness is the chief or only symptom. Some gas and some sour eructations may be complained of, but both are usually slight in the early stages. Vomiting is rare, but may be a factor. The patients have good food desire, even may have increased appetite, and many do not lose weight unless ad-vised to diet, or, finding that care in diet lessens late pain, they undereat. However, this great increase of pain due to food is usually seen later in the disease. The symptoms above given usually appear without cause known to the patient; they are often seasonal, spring or fall, though hard work, worries, and any indiscretion are sufficient to initiate an attack. During the period of attack the symptoms appear regularly from two to five hours after meals and frequently, at regular nightly intervals, varying slightly, only in each instance, and continuing until the next meal or when food is taken. Alkalies, drinks, vomiting, and irrigation ease, when resorted to, but usually food is the great remedy in early life. The time of pain is characteristic, and with the pain run the other symptoms when present. The average time of pain appearance is about

three hours after food. The time of pain and its control are almost pathognomonic. By this we mean the pain that comes from one-half to five hours after meals and is eased completely by the next meal, to appear again in from one-half to five hours—this is the characteristic feature. Quantity and quality of food may vary the time of pain, but not destroy the character. When one symptom disappears, all disappear. Diet, rest, recreation, or change of climate or vocation may relieve the attack. It usually lasts from a few days to weeks and is quite identical in symptoms day by day. The interval comes and complete relief is experienced. As time goes on the attacks become more severe, perhaps oftener and more prolonged. Greater amounts of food increase the after-coming pain, and quality makes a difference. Patients find that care in diet lessens suffering and many lose weight because of undereating. In this stage we get a history of greater or more prolonged pain, more gas, and sour, bitter eructations and often more or less vomiting. Food still gives relief in most cases, and alkalies, irrigation, and vomiting give more comfort and are more often used to bring relief than in the first stages. Vomiting or passing blood may be a factor in diagnosis, but a diagnosis of ulcer should be made without the evidence of hemorrhage, as a diagnosis of gallstones should be made before jaundice, save in those cases in which hemorrhage is the first or only symptom of ulcer, and jaundice the first and only symptom of gallstones. In this stage the symptoms, their time of appearance and control, are still usually clearly defined and a diagnosis may easily be reached.

Still later, when complications have arisen, perforations, adhesions, large ulcers, contractures, obstruction, and the like, the symptoms may take on varied hues and we are at a loss, unless we have been careful to get out early definite history. The symptoms now may be greatly prolonged, never quite clearing up, or they may be continuous with gradually increasing invalidism. Pain increased or not eased by food, food soon adding to distress, sour, bitter, burning eructations and vomiting of large quantities, loss of weight, decided obstruction and cachexia may be present. Vomiting, irrigation, and alkalies usually bring some degree of ease. The history is always that of the stomach and we can usually by exclusion reach a respectable diagnosis. The early history is here a great illuminating factor, and the roentgen ray is a comfort, as it is, indeed, in all the stages of peptic ulcer.

Such a history, more or less modified in each case, gives us evidence

to warrant a clear diagnosis of peptic ulcer in 80 per cent of cases, while in another 9 per cent the diagnosis of ulcer figures strongly, with gallstones, appendicitis, or cancer not always clearly differentiated. It must not be forgotten that latency of ulcer as well as latency of gallstones is to be considered when clearing up our diagnostic statistics. Certain it is that both may be latent for years even, and discovered only at operation, by the roentgen ray or at autopsy. In ulcer the first and only symptom may be hemorrhage, more or less severe and repeated, or the pain of perforation may be the first warning. Again, symptoms of decided obstruction may first come to attention and thus the late complicated history is ushered in, never in any period possessing the early signs, or showing them so little that the patient had not made complaint or sought relief. The clinician who carefully bears latency in mind may reach happier conclusions, and the surgeon who gives this point attention will be safer to trust and will get better results. The late complicated stage of ulcer often loses its type and merges into the signs of any gastric disturbance, which may be due to lesions outside, to focal infection, or to general diseases, yet careful, detailed histories clear up many difficult cases. The early history brings other evidence, while the x-ray may add still further light.

There is a class of ulcer cases not so large but quite distinctive and extremely difficult to diagnose. Clinically they are diagnosed gallstones. These ulcers are often duodenal or pyloric but may be gastric. They seem to have no complication save frequent perforating tendencies, yet a part are not so reported at operation. Often the only symptom complained of is sudden, acute short attacks of epigastric pain, rarely with radiation, but which may radiate to the back if posterior perforation is impending. Recovery from pain is usually sudden and complete, typically gallstone in character, and no other rational diagnosis can be made save by the x-ray. In the group of cases under discussion the roentgen ray and the surgeon must disclose the condition, or, when no operation is done, characteristic symptoms develop later. In the larger group of chronic, complicated ulcer cases with perforation the early history often gives the solution.

Gallstones.—There is a train of symptoms quite peculiar to gallstone disease. In cholecystitis the symptoms may quite simulate cholelithiasis, or, again, vague symptoms only may point to the liver, while the gastric disturbances predominate. The large majority of attacks, however, are rather easily diagnosed. The symptoms are made up of

practically the same elements as in ulcer,—pain, gas, and vomiting,— chronically periodic in a sense; but the grouping is quite different. Here the symptoms appear in acute attacks of short duration, usually from a few moments to hours, but one such attack is the rule with an intermission of hours, days, months, or years of normal health, if the case is a simple uncomplicated one. The attack comes suddenly, often without any warning. Quite as characteristic as this suddenness of onset is the abrupt cessation, even at the height of pain, followed by immediate return to health. Pain is the great and constant symptom. It is more often epigastric though it may radiate to the right arch and to the back. The chest and abdomen may be included in its severe grasp. It is boring, pressing, a "queer agony" often expressing the sensations, or it may be lancinating, severe, and terrific, approaching the pain of gastric perforation. Spasm of the diaphragm is marked in severe cases, but may be slight or absent in the less severe attacks. Pain appears without relation to food in the greater number of cases, coming before meals, after meals, or when abstaining. It is quite independent of food, not caused or relieved by food in the majority of cases, and the patient rarely speaks of food in relation to pain. The gas present intensifies the distress, as belching often gives short relief, but the bloated, distended, bursting sensation that so many patients experience is due to the character of the pain, its field of radiation, and the spasm, rather than to the actual gas present. Vomiting in uncomplicated gallstone cases is quite as infrequent as in cases of uncomplicated gastric ulcer. It comes at the height of pain, consists of green or yellowish fluid, usually small in quantity, and gives short relief, or permanent cessation of pain may follow it. It is usually not prolonged and, unless food is present, is not copious.

Two smaller classes of quite distinct cases should be mentioned. The first is exemplified by rather mild digestive disturbance, often considered lightly by both patient and physician. There are slight attacks of distress from gas or pressure, coming oftenest at irregular times, but again with some relation to food. These are of sudden onset, short duration, and eased by eructations of gas, or slight regurgitations or vomiting. Again they pass off almost unnoticed without great disturbance or any treatment. The usual return to health is noted, as in our typical class, and these dyspeptic mild attacks are just as characteristic of gallstones as are the severe attacks which usually supplant the mild. They are of the same type, yet the one is named gallstones

and the other dyspepsia.   The other class of cases is that of chronic gallbladder trouble with adhesions, duct obstruction, perforations, duct infections, contraction, and perhaps pancreatitis.   When this condition obtains, chronic gastric disturbances often are foremost, the acute pain is like chronic gastric perforation, and the whole picture is so closely that of chronic ulcer with perforating complications that a differential diagnosis cannot be made if only the present symptoms are considered. The key to diagnosis lies in developing the early history which often clearly shows the early clear-cut ulcer syndrome or the typical train of gallstone symptoms.   However, this differential diagnosis is not now the important point.   These patients are essentially surgical, and a surgical diagnosis and an experienced surgeon usually set things right.

If we understand the regular characteristics of the period of attacks of ulcer, the day-by-day symptoms, coming from two to five hours after meals, and eased by food, drinks, alkalies, vomiting or irrigation, and if we as clearly recognize the irregularity of the gallstone attack, not due to or eased by food, suddenness of appearance and disappearance, and the perfect health until attacks recur, hours, days, or months later, we shall have arrived at a state wherein we may easily diagnose 80 per cent of ulcer cases and about 86 per cent of gallstone disease.

The following considerations may help when doubt exists and symptoms mix: The percentage of perforation in chronic ulcer is quite large (twenty-six) and it is in this group we find our greatest number of errors. We call the cases gallstone disease or at least partly divide the diagnosis with gallstones.

Jaundice is frequent with gallstones (25 per cent) and hemorrhage in ulcer (25 per cent).   Vomiting is not common in either condition early. It is bitter and greenish-yellow in gallstone disease; in ulcer it is clear and sour or a clear, tasteless or a salty fluid coming up as an eructation. Late, it is more copious in ulcer and more often contains blood, though in the latter condition the symptoms of vomiting help but little in differential diagnosis.   A rapidly developing constipation is a clear-cut symptom in ulcer, not in gallstones.   This is especially true in men. Food remnants and bacterial elements found on irrigation are ulcer signs, more rarely found in gallstone disease.

Ulcers are most common among the young, or, perhaps better, histories of chronic ulcer lead us back to the early life of the patient.   When other things are equal so far as symptoms are concerned, and a question of gallstones or ulcer arises, let the date of first symptoms decide.   If

symptoms began when the patient was young (fifteen to twenty-five or thirty), let the diagnosis of ulcer be favored, if in late life, give that of gallstones the preference. Latent ulcers are not so apt to be carried over into late life as are latent gallstones.

When attacks come two or more times a day, repeated in a measure day by day, without food relation, even when acute, like gallstones, guard carefully the diagnosis. It is much oftener ulcer with perforation than gallstones. With gastric symptoms attendant, yet not quite surely ulcer, go back for aid in your histories to the early period of attacks.

With pain repeating acutely night after night, with more or less constant distress along with other gastric symptoms, call it ulcer, unless chills, fever, or jaundice make gallbladder affection probable. If a patient from thirty-five to fifty years of age has had digestive troubles for years and has not developed jaundice, fever, chills, or a large liver, diagnose ulcer, especially if the acids are high.

In general, acids are higher in ulcer than in gallbladder disease and aid in diagnosis. Usually a history that early is typical of ulcer or gallstones may later be too irregular for a diagnosis; thus we learn to depend on early symptoms. In the presence of perforative symptoms the clinician is quite apt to lean, at least secondarily, to a gallstone diagnosis, even when the symptoms are prolonged and many of them are clearly of ulcer. In prolonged spells, with burning attacks daily, ulcer, not cholecystitis, is the rule. When there is a faint, weak feeling with an empty stomach, which is even slightly relieved by lightest foods and drinks, diagnose ulcer even in the presence of other formidable symptoms. The pain of ulcer is more apt to radiate low than is that of gallstones; rarely is gallbladder pain low. With sharp, gallbladder-like pain preceded for a time by indigestion, consider first ulcer with perforation.

Work, worry, and fatigue often initiate an ulcer attack—rarely do they excite one of the gallbladder. Pressure, position, and reclining may ease ulcer pain, rarely gallstone pain. Acids have a value. With prolonged spells, pain, vomiting, and other things equal, the higher acids point to ulcer.

Pain that comes immediately or soon after food, with little or no food or soda relief or but transitory relief, does not make an ulcer history clear enough for diagnosis, but appendicitis and cholecystitis might be considered, though not urged.

With varying spells of short (three days), irregular food distress or pain, no appetite, even with gas belching and vomiting and good acid content—look out for appendicitis. Appendicitis gives a gastric history or gastric symptoms, but not an ulcer syndrome.

Young patients usually have clear-cut peptic ulcer histories or symptoms that seem clearly like gallstones, but are really ulcer (perforating). Complicating difficulties are more often seen later.

Nausea is not a common ulcer symptom. A patient with ulcer vomits because of pain, burning, or distress. Nausea may come later, and frequently occurs when vomiting is enhanced, due to adhesions, contractions, and obstruction, but usually in ulcer vomiting is not associated with great nausea. Nausea is frequently met in gallstone disturbance and may be intense, though it is oftener caused by extrinsic disease other than gallstones (appendicitis, tuberculosis, etc.).

Many diseases give gas, sour stomach, eructations, and vomiting, therefore soda ease must find other corroborative evidence to weigh heavily in a diagnosis of ulcer.

Another point to be held clearly in mind by both clinician and roentgenologist is that when there are many inflammatory adhesions about the gallbladder, pylorus, and duodenum, there is often deformity and obstruction to mislead the roentgenologist, and quite enough to give decided gastric symptoms. Then if the gallbladder is the real lesion, we may have added the dyspeptic symptoms thus induced and the whole picture will be clearly that of ulcer, both from the standpoint of the roentgen ray and the history. Such diagnosis is warranted; it is the logical one, and reflects on none of those who make it.

The x-ray lessens such errors in diagnosis when the clinician turns to it for help. If symptoms are properly interpreted, if the roentgenogram has been skilfully read and both findings wisely correlated, a fewer number of ulcer cases will slip by on a gallstone diagnosis.

The roentgen ray is the great modern boon to gastric diagnosis—the real comfort to the clinician who plods along, discussing histories, and no one should appreciate its value or its limitations half so much as the clinician. Roentgenography has its limitations, but it opens up a wonderful field of possibilities. It has improved gastric diagnosis, it has stimulated the writers of clinical histories to better service. Who has not determined to do more careful history writing, interpreting, and summarizing when the x-ray has upset the diagnosis? What clinician has not felt the great relief of certainty when the ray has shown a lesion

after the history had failed to get the coveted symptoms? And, too, when the history has been clear and the ray has located the lesion, who has not felt that comforting assurance that he could approach his patient quite fully equipped to advise treatment, readily, more willingly, and more completely? A closer coöperation between the roentgenologist and the clinician will mean a better interpretation of symptoms and methods, and a clearer correlation of all. Indeed, this close coöperation promises such advances in the near future that gastric diagnosis will have less for which to apologize.

ROENTGEN DIAGNOSIS OF CONCURRENT GASTRIC AND DUODENAL ULCER*

R. D. CARMAN

The object of this paper is to call attention to the frequent concurrence of gastric and duodenal ulcer and the possibility of discovering both conditions in a given instance with the roentgen ray.

In the Mayo Clinic, during the year of 1916, sixteen patients were found at operation to have both gastric and duodenal ulcers. In this same year the total number of cases of gastric ulcer in which operation was performed was 139 and the total number of cases of duodenal ulcer was 490. In other words, 11.5 per cent of the patients having gastric ulcer had duodenal ulcer also, and 3.2 per cent of the patients with duodenal ulcer had associated gastric ulcers. The diagnosis of these lesions when they coexist is, therefore, of some practical moment.

A purely clinical diagnosis, or rather, a diagnosis independent of roentgen assistance, is obviously not feasible. Even when either condition exists alone the clinical differentiation between them is often impossible, and the roentgen ray is commonly utilized as an aid. Likewise, when both lesions are present we are usually obliged to depend on the roentgen examination to establish the fact.

The 16 patients mentioned were all examined by the roentgen ray. Frank admission must be made that in only 7 of these was the presence of both lesions discovered by the roentgen examination. However, for reasons that will be set forth, it is probable that this small number does not fairly represent the limits of efficiency of the roentgen method. In 2 cases diagnoses of gastric ulcer alone were made, in 6 cases, of duodenal ulcer alone, and in 1 case the diagnosis was gastric cancer. Thus in all of the 16 cases there were roentgen signs of a pathologic condition, and with the one exception correct diagnoses were made either wholly or in part.

The roentgen signs of gastric and duodenal ulcer include phenomena
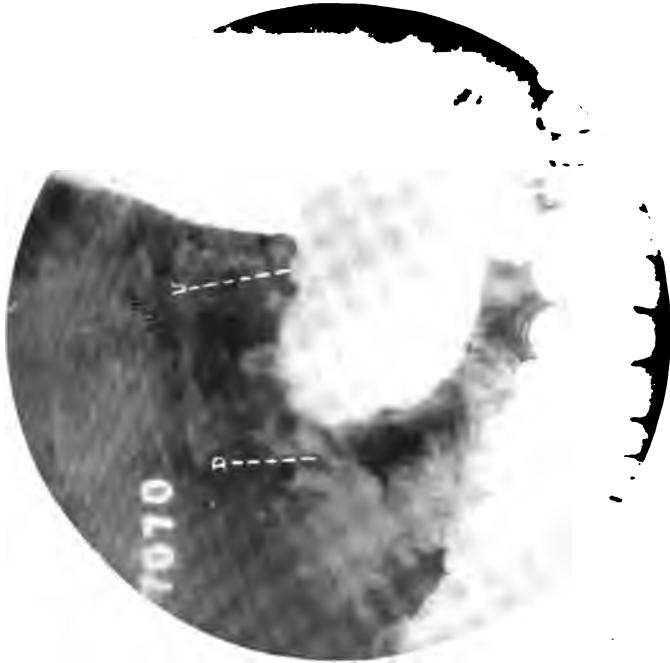
Fig. 16.—U and D, note Figs. 13 and 14.
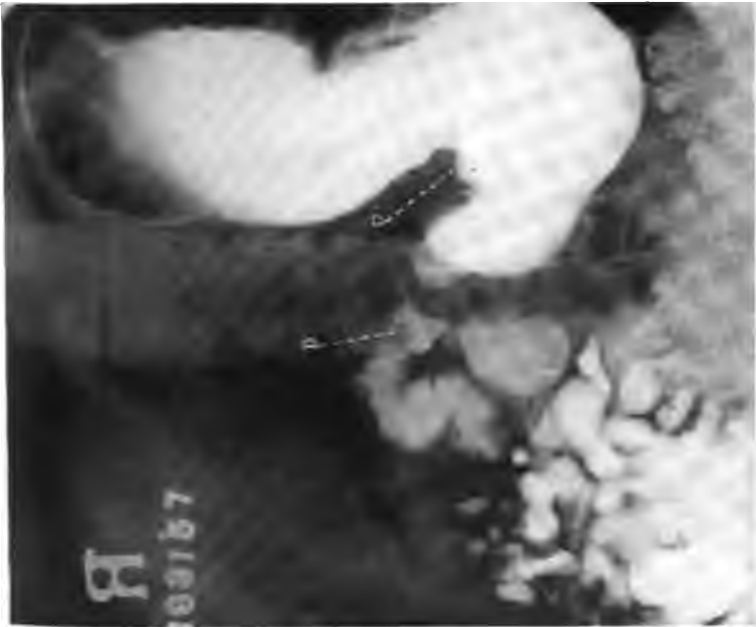
Fig. 15.—U and D, note Figs. 13 and 14

CANCER OF THE STOMACH*

W. J. MAYO

More than 30 per cent of all cancers in civilized man are in the stomach. Why should there be such an enormous percentage of cancers of the stomach? This manifestation of malignant disease is uncommon in lower animals and primitive man, yet there is comparatively no essential secretory or mechanical difference in the function or structure of the stomach. It has been suggested that the disease is connected with the formation of an acid secretion. As far as I know, no gland in the human body secretes an acid. In the colon the acidity is not a secretion of the mucous membrane, but is due to bacterial action. The kidney has no true secretion; it is a filter from which acid-forming bodies are excreted. The stomach does not secrete acid; the material for the formation of acid is brought together on the surface of the mucous membrane and the acid is formed not within but outside the glands. Acidity of secretion and changes incident to disturbed storage function may be contributory factors, but evidently they are not the responsible agents.

Does the cause concern food or drink? The difference in the nature of the food and drink of lower animals, primitive man, and civilized man is not sufficiently great to lead to the belief that food or drink of themselves could be looked upon as the important factors.

May it not be some process to which civilized man subjects food or his manner of partaking it that is the exciting agent? The only known fact regarding the causation of cancer is the influence of chronic irritation on its production. Whenever cancer exists in one species of animal or race of men in an enormous excess of what occurs in other animals or other races of men, it has been found owing to a single cause. Were there many causes, some would be operative among all.

The relation of chronic irritation to the more familiar forms of cancer is an interesting study. For instance, I have been able to find some

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evidence that cancer of the breast was an extremely rare disease in all races of people in whom the entire breast was left uncovered and exposed to the air, and that the frequency of this manifestation of malignancy was in proportion to the covering of the breast and the pressure exerted by the covering.

The theory that the frequency of cancer of the stomach in civilized man is the result of hot food and drinks which act to cause chronic irritation of the gastric mucosa is worthy of consideration. The infrequency of malignant disease of the stomach in animals and primitive man would then be explained by the fact that they take their food and drinks cold. At the general meeting of the American Medical Association in 1912[2] I called attention to the possibility that hot drinks might be the exciting agent, and during the past two years further investigation of the circumstantial evidence related to the facts leads me to believe that it may be one if not the main cause of the tissue-changes which precede cancer of the stomach.

Why should cancer of the stomach be more frequent in the male (38 per cent) than in the female (22 per cent)? A possible answer to this question is furnished in the frequency of cancer of the posterior wall of the pharynx and upper gullet in Chinese men, who are served first while the rice is hot; the women eat at the second table, when the rice is cold, and rarely have cancer in this region. It is the social custom of modern civilization for the lady of the house to serve the beverages—herself last.

That heat has a remarkable influence in the production of chronic irritation has been known from the beginning of observations on cancers. Smokers' cancer of the lip, for obvious reasons, is almost confined to the male sex. The Kangri burn cancer of the Kashmir natives comprise more than half of the cancer of this race. They carry a clay charcoal burner in a wicker basket across the lower abdomen when they go into the mountains and, as a result, have heat irritation which acts to cause cancer of the lower abdomen and groins.

Here again the disease is largely among men because they are most frequently subjected to this form of tissue-insult. Locomotive engineers who are for years subjected to the prolonged heat of the fire-box have cancer of the shins arising from chronic heat irritation. Cancer of the skin of the face, which occurs so frequently among Australians that it is often called the Australian disease, begins in a peculiar climatic heat irritation.

A high percentage of persons take their drinks hotter than can be borne comfortably in the mouth. It has been shown by x-ray workers that when the stomach contains much food and drinks are taken, these drinks are not carried directly into the cavity of the stomach, but, by a peculiar muscular contraction a canal (canaliculus gastricus) is formed in the lesser curvature along which the fluids are rapidly passed into the duodenum. Eighty-five per cent of all cancers and ulcers of the stomach involve the lesser curvature, and they may have a common cause. The mouth and gullet are protected by pavement epithelium and possess sensitive nerves which give warning of injury; the stomach has no such protection.

Newer and better methods of diagnosis within the past few years have greatly extended operability and made possible radical procedures in an increasing number of patients. The early diagnosis of cancer of the stomach depends on the roentgen examination. Carman has shown that cancer of the stomach may be demonstrated in 95 per cent of cases in this way by the time they give sufficient evidence of their presence to call the patient's attention to the fact that something is wrong. Every person in whom there is suspicion of cancer of the stomach should be promptly subjected to examination by the roentgen ray. All persons with an anemia which cannot be otherwise explained should be subjected to such examination. Cancer of the body of the stomach and cancer of the cecum and ascending colon may produce striking anemias early, before there are local symptoms.

Mechanical conditions arising from the frequency with which the disease originates in the pyloric end of the stomach is a fortunate occurrence and leads to early diagnosis. The presence of a movable tumor in this situation, even of considerable size, is a favorable indication and not, as it is so frequently looked upon, a sign of inoperability. If the cancer as it appears in the stomach is mechanically removable, even if all the glands and indurated tissue cannot be removed, I believe resection is still advisable. The mortality will be very little higher than after gastro-enterostomy, palliation will be many times greater, and occasionally a patient will be cured. I have never forgotten a lesson learned from a search of our statistics on gastro-enterostomy for the palliation of clinically inoperable cancer of the stomach, in which a section had not been removed for microscopic examination. Five of the patients operated on in this manner lived more than five years, showing that a clinical diagnosis of inoperable cancer is open to error.

Chronic ulcer of the stomach is not often cured medically, and I am convinced it is a potential source of gastric cancer. We cannot question the fact that in the past many patients have been treated for the diagnosis of ulcer, not for the disease. When ulcer is shown in the roentgenograms, other things being equal, it should be removed by actual excision and gastro-enterostomy, which gives a mortality of about 5 per cent; or better, after the removal of tissue for microscopic examination by frozen section, the ulcer should be burned out with the cautery after the method of Balfour,[1] and followed by gastro-enterostomy. There were but two deaths in 198 operations by the latter method (a mortality of about 1 per cent).

In cases of cancer of the pylorus, resection by the second method of Billroth leaves little to be desired. For cancerous ulcers high up on the body of the stomach, occasionally a resection in continuity (segmental resection) may be indicated, but for cancer of the pyloric end of the stomach and lesser curvature, which constitute the great majority of cases, wide removal followed by closure of the end of the duodenum and direct anastomosis between the cut end of the stomach and the side of the jejunum—antecolic—is the operation of choice. This method extends operability, and enables the speedy removal of growths which would not be operable by any other method with which I am acquainted. On a number of occasions the operation has been completed in less than forty minutes.

The posterior end-to-side operation as first described and practised did not produce better operative mortality statistics than the Billroth No. 2, but it did increase operability. The cause of the mortality in the posterior method (end of the stomach with the side of the jejunum) concerned the transverse colon and transverse mesocolon. It was difficult, consumed time, and occasionally it was impossible to fasten the anastomosed area below the opening in the transverse mesocolon. If this was not done, the mechanical conditions often proved unsatisfactory. By the antecolic method a length of jejunum, sufficient for a free loop (16 to 18 inches), is passed around the omentum and transverse colon, and easily brought to the gastric stump for anastomosis. By this method it was found possible to reach a point for section still higher on the stomach than by any previous method, and the mortality dropped from 13.2 per cent average to 6 per cent in an equally advanced or even more advanced group of cases.

Some of the operations in our series were very extensive. In nine

cases the resections were subtotal, that is, the whole of the stomach was removed, except just enough to enable an anastomosis to be made. In one instance I removed the entire stomach by the Moynihan method and with it a margin of the esophagus. The patient made an excellent recovery and has surprisingly good function.

What results may be expected from radical operations for cancer of the stomach? We have eliminated all resections of the stomach made previous to 1897, as up to that time a specimen was not regularly subjected to microscopic examination. Taking the twenty years from October 10, 1897, to October 10, 1917, there were 651 resections of the stomach for cancer. Of 427 patients operated on more than three years ago who recovered from the operation, 311 have been traced; 120 (38.6 per cent) were alive three years or more after operation. Of 313 patients who were operated on more than five years ago, 239 who recovered from the operation were traced, and 62 (26 per cent) of these were alive five years or more after operation. In compiling these statistics we have assumed that the deaths which occurred were from recurrence of cancer. This assumption is unwarranted, as the Medico-Actuarial Mortality Investigation Tables show a normal death-rate at the average age of these patients (fifty-two years) of 4.2 per cent for a three-year period and 7.5 per cent for a five-year period. These percentages, so far as the cure of cancer is concerned, could be fairly subtracted from the death-rate and add by so much to the percentage of cures. It has been our experience that the patients we have not been able to trace following operation and whose ultimate condition has been ascertained in after years have shown a higher than average percentage of cures. No special effort was made to trace patients after the five-year period, but incidentally it was learned that 35 lived six years or more after operation, 27 lived seven years or more after operation, 18 lived eight years or more, 10 lived nine years or more, 7 lived ten years or more, 5 lived eleven years or more, 3 lived twelve years or more, and one lived more than fifteen years after operation. These statistics of actual cures compare favorably with those of cancer in other parts of the body and show that the radical treatment of cancer of the stomach is keeping pace with the modern treatment of cancer in general.

REFERENCES

1. Balfour, D. C.: Restoration of gastro-intestinal continuity by means of antecolic gastrojejunostomy following partial gastrectomy for cancer of the pyloric end of the stomach. Surg., Gynec. and Obst., 1917, xxv, 473–477.
2. Commemoration Volume, Amer. Med. Assn., 1915, p. 310.

THE SURGICAL SIGNIFICANCE OF GASTRIC HEMORRHAGE*

D. C. BALFOUR

From a surgical standpoint, hematemesis is caused by, or occurs with, first, primary lesions in the stomach and duodenum, such as ulcer, cancer, tuberculosis, syphilis, and benign tumors; and second, certain diseases and infections which are not necessarily associated with recognizable changes in the gastric mucosa.

In the first group, namely, those cases in which there is a chronic gastric or duodenal lesion, both diagnosis and treatment are on a relatively satisfactory basis, and the general surgical principles applicable in the treatment of the most common cause of hematemesis in the group, that is, gastric or duodenal ulcer, are more or less accepted. These bleeding ulcers may be conveniently divided into two groups, namely, those ulcers in which there has been a history of bleeding, and those in which active bleeding is taking place.

1. The indications for surgical treatment of the patient with a history of single or recurring gastric hemorrhages in whom a diagnosis of ulcer can be established are positive. It has been our experience that to depend on gastro-enterostomy alone for the treatment of ulcer which has been associated with bleeding is to court recurrence of the hemorrhage, and that to obviate further hemorrhages, excision, preferably by cautery or resection of the ulcer, is imperative.

2. The management of the ulcer which is the cause of continuous, active bleeding has been the subject of considerable controversy. There are no means of estimating the size of the bleeding vessel. As a single gastric ulcer hemorrhage is rarely fatal, the margin of safety usually permits delay until lowered blood-pressure has allowed clotting to take place. Death due to hemorrhage from gastric ulcer has usually been the result of repeated hemorrhages at comparatively short intervals. A

recurrence of bleeding, therefore, a few days after a serious hemorrhage is more than a sufficient indication for operating during the active hemorrhage, rather than to risk further delay. In repeated or continuous small hemorrhages, which do not threaten the life of the patient, transfusion has proved of the greatest value, not only in controlling the bleeding by the introduction of the necessary elements for clotting, but also adding greatly to the safety of later operative measures for the ulcer.

In the second group of cases of hematemesis, namely, the cases in which there is no surgical lesion in the stomach, a variety of diseases and conditions call for consideration, and they may advantageously be divided into groups as follows:

1. Cases in which there are recognizable changes in the liver or spleen or both; a group in which hepatic cirrhosis and splenic anemia are representative.

2. Cases in which a chronic infective focus, such as a diseased appendix or gallbladder, is apparently responsible for the bleeding.

3. A group which includes, in the main, such acute infections as typhoid, pneumonia, etc.; multiple hemorrhagic erosions; cases in which no changes can be demonstrated either at necropsy or operation, and the cases of "gastrostaxis" of Hale White.

The differential diagnosis of these various groups is not made without difficulty, and the ordinary difficulties are exaggerated by the fact that many conditions, such as hepatic cirrhosis, appendicitis, or gallbladder disease, are associated with disturbances in gastric digestion, which may easily be misinterpreted as due to ulcer. Hematemesis added to such a syndrome has not infrequently resulted in unnecessary and unsuccessful operations based on an erroneous diagnosis of gastric ulcer.

Hepatic cirrhosis and splenic anemia are relatively often the cause of hematemesis in this extrinsic group, and if one bears in mind the ease with which mucosal hemorrhages take place in these diseases, and the fact that such hemorrhages have the same characteristics as those associated with the other more or less obscure causes in the group, it seems to be suggested that the liver or spleen or both offer a key to the explanation as to the manner in which many, if not all, these mysterious hemorrhages take place.

The close association of the spleen and the liver, both in the normal physiologic and anatomic relationship, and in disease processes, necessitates the most careful consideration of the spleen in all conditions which involve the portal circulation. It must be remembered, too, that the

spleen, or liver, or both, may be responsible for gastric hemorrhage, and yet themselves not exhibit any evidences of disease. I recently published the history of a case in which I removed a slightly enlarged spleen, chiefly on an empirical basis, from a patient who had had various operations, mainly gastric, in an effort to find the cause of, and to prevent, gastro-intestinal bleeding. This patient has had no bleeding since the splenectomy. Various writers, particularly Rolleston,[1] have attributed gastric hemorrhage in such cases to a "latent" hepatic cirrhosis.

The treatment by splenectomy of moderately advanced hepatic cirrhosis is as yet in the experimental stage. The disease is usually so slowly progressive that even though the immediate results have been satisfactory, we do not feel justified in drawing conclusions from the cases in which we have performed splenectomy. Nevertheless, there appears to be a definite group of so-called primary hepatic cirrhoses produced by toxins originating in, or elaborated in, the spleen. So in those cases in which hematemesis occurs in what might be termed the precirrhotic stage of hepatic cirrhosis, that is, when the cirrhotic changes are scarcely visible either grossly or microscopically, splenectomy may be indicated, if the spleen is large. Under such circumstances the operation may be looked on as probably a curative measure.

It is a significant fact that in those cases of gastric hemorrhage which show only slight erosions in the mucosa of the stomach, microörganisms may be obtained from the depths of the erosions and the same organisms may be obtained from the spleen (Rosenow[2]); moreover, it has been shown that various forms of encapsulated bacilli will produce gastric and intestinal hemorrhages. These bacteria, although differing in some respects, have one power in common, namely, the power to exert a "specific effect on blood-vessels and produce changes in the blood itself." Litzenberg early reported the recovery of the bacillus of Friedländer from hemorrhagic areas in the mucosa of the stomach and intestine of a child dying from gastro-intestinal hemorrhage. We know also that in certain cases of syphilis associated with anemia the spleen contains spirochetes in large numbers (Giffin[3]). The liver, deriving as it does a large quantity of its blood from the spleen, has every opportunity for picking up toxins and bacteria from the spleen. Thus the spleen must also be recognized as a possible causative factor, not only of changes in the liver, but directly or indirectly, of gastric hemorrhage.

In recurring gastric hemorrhage in which demonstrable lesions in the stomach or duodenum are not present, and other extrinsic causes have

been excluded, the rôle of the spleen should be investigated. It is even possible that in such cases when bleeding is sufficient to endanger the patient's life and when the primary focus of infection is not determined, splenectomy (if the spleen is enlarged) may be an indication by reason of the mechanical influence of lessening the venous return to the stomach.

The group of cases in which there is an obvious focus of infection includes cholecystitis, pancreatitis, salpingitis, tuberculous peritonitis, and appendicitis. In these and other conditions, gastric hemorrhage may occur, and not only is a positive diagnosis usually possible, but treatment as a rule is successful.

Several cases of gastric hemorrhage have been observed in our clinic in which there was well-marked appendicitis, and appendectomy seemed to show that the appendix had been the primary cause of the bleeding. Moynihan[4] early drew attention to this fact. Eusterman[5] has shown that about 2 per cent of appendix cases and about 5 per cent of gall-bladder cases with marked reflex gastric symptoms gave a history of previous bleeding. The spleen also may act as a primary focus of infection, although our present knowledge would indicate that it acts rather as a medium through which infection from a distant focus is transmitted to the liver.

The group of cases in which fatal or serious gastric hemorrhage occurs and no cause can be demonstrated has been the subject of much controversy. Unless the primary cause for such hemorrhage is found, surgical treatment is not clearly indicated, and the same statement is true regarding those acute infections, such as typhoid, pneumonia, and in cases of mucous erosions which are so often multiple and occasionally seen at necropsy.

In reviewing these various groups, there are several facts which strongly suggest that gastric hemorrhage may be produced through the same channel in all, namely, the portal circulation. We know, for example, that hepatic cirrhosis is a frequent cause of hematemesis; that hepatic cirrhosis is often toxic in origin (Adami[6]); that a large part of the blood of the body is transmitted through the liver; and that toxic foci which are associated with gastric hemorrhage are found, especially in the abdomen. Is it not possible that these various focal infections produce chemical or physiologic changes in the liver, changes which, if the cause is not eradicated, progress to the cirrhotic liver? It would seem further possible that the liver under such circumstances may in some manner sufficiently lower the resistance of the gastric mucosa to

permit the bacteria, which are consistently present in both true gastric ulcer and in mucous erosions, and which may reach the stomach either by the blood stream or by the food, to set up those diffuse or localized tissue changes.

In other words, it is probable in many of these gastric hemorrhages in which a primary causative focus is established, that the conditions which result in hematemesis are largely under the control of the liver; and since the spleen is so intimately concerned in the functions of the liver, it, too, must be looked on as an important factor.

RECAPITULATION

It should be emphasized that the surgical significance of gastric hemorrhage demands:

1. The proof that a gastric hemorrhage has taken place.

2. The determination and eradication of the originating cause, whether chronic surgical lesions in the stomach, or extrinsic foci.

3. The treatment of the hemorrhage per se, the general indication being to carry out operative treatment during the interval between hemorrhages.

4. The recognition of the possibility that many of the extrinsic causes of gastric hemorrhage are toxic in nature, and that the infection takes place by means of the portal circulation through the liver.

5. That not only is the liver of first importance in these heretofore unexplained hemorrhages, but the spleen, by reason of its close association with the liver, is probably an important factor in the problem.[7]

REFERENCES

1. Rolleston, H. D.: Diseases of the liver, gallbladder and bile ducts, London, Macmillan, 1914, p. 268.
2. Rosenow, E. C.: Personal communication to the author.
3. Giffin, H. Z.: The treatment by splenectomy of splenomegaly with anemia associated with syphilis, Am. Jour. Med. Sc., 1916, clii, 5–16.
4. Moynihan, B. G. A.: Appendix dyspepsia, Brit. Med. Jour., 1910, i, 241–244.
5. Eusterman, G. B.: Incidence and diagnostic value of blood or hemorrhage in gastric and intestinal lesions, a clinical and statistical study, St. Paul Med. Jour., 1913, xx, 587–593.
6. Adami, J. G., and Nicholls, A. G.: Principles of pathology, Philadelphia, Lea and Febiger, 1909, iii, 466.
7. In addition to the references cited in the text, the following will be found of interest:
    Balfour, D. C.: Splenectomy for repeated gastro-intestinal hemorrhages, Ann. Surg., 1917, lxv, 89–94.
    Armstrong, G. E., and Mullaly, E.: Fatal gastro-intestinal hemorrhage, Am. Jour. Med. Sc., 1914, cxlvii, 803–809.
    Litzenberg, J. C.; discussion, McClanahan, H.: Hemorrhage in the newborn, Jour. Am. Med. Assn., 1906, xlvii, 1147.
    Mayo, W. J.: Ulcer of the stomach and duodenum, with special reference to end-results, Ann. Surg., 1911, liv, 313–320.
    White, W. H.: Gastrostaxis, or oozing of blood from the mucous membrane of the stomach, Lancet, 1910, ii, 1125–1189.

GASTRODUODENOSTOMY—ITS INDICATIONS AND TECHNIC*

D. C. BALFOUR

Gastric surgery has attained its present high place as a result not only of the impetus received from the early contributions of American and English surgeons, but also from an increasing coöperation between clinician, roentgenologist, and surgeon, the investigation of the causes of past failures, a clearer conception of the indications for operation, the more careful observance of general surgical principles; and particularly a more intelligent appreciation of the specific merits of the many technical procedures, old and new, which are at the disposal of the surgeon in the treatment of benign gastric and duodenal lesions. Further progress can well be expected as the experience of those who are particularly interested in the subject of gastric surgery becomes available, and it is with this in mind that I draw attention to the operation of gastroduodenostomy.

Gastroduodenostomy is not an infrequent operation, inasmuch as the various types of pyloroplasties (Finney, Heinecke, Mikulicz, etc.) are essentially anastomoses between stomach and duodenum. The operation to which I have reference does not include in its technic any interference with the pylorus, nor does it utilize the ulcer callus as any part of the posterior wall of the anastomosis. In other words, the ulcer area is purposely avoided and the anastomosis is made entirely in healthy tissue.

Historically the operation of gastroduodenostomy is of some interest.

Moynihan credits Jaboulay as the first to suggest and carry out gastroduodenostomy (1892 and 1894). Many modifications of this principle have been proposed. Kümmell divided the duodenum, closed the proximal end, and implanted the distal into the anterior wall of the stomach near the greater curvature. Billroth, Villard, Terrier, and Kocher devised other methods of accomplishing the operation. Kocher

advised an elaborate mobilization of the duodenum (the descending and a considerable portion of the transverse colon) by dividing the parietal peritoneum covering the kidney. The operation he named "lateral gastroduodenostomy." In this country by far the most popular form of this principle has been the pyloroplasty of Finney, an operation which has the advantage of permitting under certain conditions the safe excision of the ulcer, as well as making possible the inspection of the mucosa in the immediate vicinity of the pylorus.

It is important to become familiar with these various methods and to know their indications. For only with such knowledge will the error of forcing a favored operation to apply to unsuitable conditions be avoided. The circumstances we have recognized as justifying a gastroduodenostomy of the type described herein are as follows:

1. A pyloric lesion or a lesion involving the pylorus, associated with marked obstruction, with more or less ballooning of the duodenum, producing a deformity the counterpart of an hour-glass stomach (Figs. 19 and 20). Particularly if such a lesion is active or has caused the pylorus to become fixed to pancreas or liver, or in a mass of adhesions, should the advisability of gastroduodenostomy be taken into consideration. At the same time we would still give posterior gastrojejunostomy the preference in this group, with gastroduodenostomy as an excellent alternative, reserving the latter as the operation of choice in the groups to follow.

2. Any condition such as those indicated in Group 1, complicated by anatomic derangements (either congenital or the result of previous inflammatory exudate) of a nature to preclude or make inadvisable a posterior gastrojejunostomy.

3. In those instances in which patients have failed to obtain the expected relief from gastrojejunostomy because of secondary complications, such as gastrojejunal ulcer and mechanical difficulties, because the operation was ill-advised or improperly done, or because of unknown reasons. In such cases gastroduodenostomy has been of signal value following the cutting-off of the gastrojejunostomy and the restoration of the walls of the stomach and jejunum.

It should be mentioned that the lesion in these various conditions, as far as can be determined, is a chronic ulcer, that it is not safely excisable, and that conditions are such that a pylorectomy is not justified because of the operative risk. Our operation is carried out as follows:

The best possible exposure and mobilization of the pyloric end of

Fig. 19.—High-lying duodenal ulcer causing an angulation which brings the upper duodenum and the pyloric end of the stomach in close apposition. Gastroduodenostomy made below ulcer and ulcer covered. (See Fig. 20.)

the stomach and duodenum is obtained.   In many cases this exposure
is already strikingly in evidence, while in others much aid may be
gained from the careful division of the adhesions which course over the
prospective field of operation.   Markers are now placed close to the
inferior border of the duodenum and stomach at such points as to
insure, when approximated, a sufficiently large anastomosis.   A line of
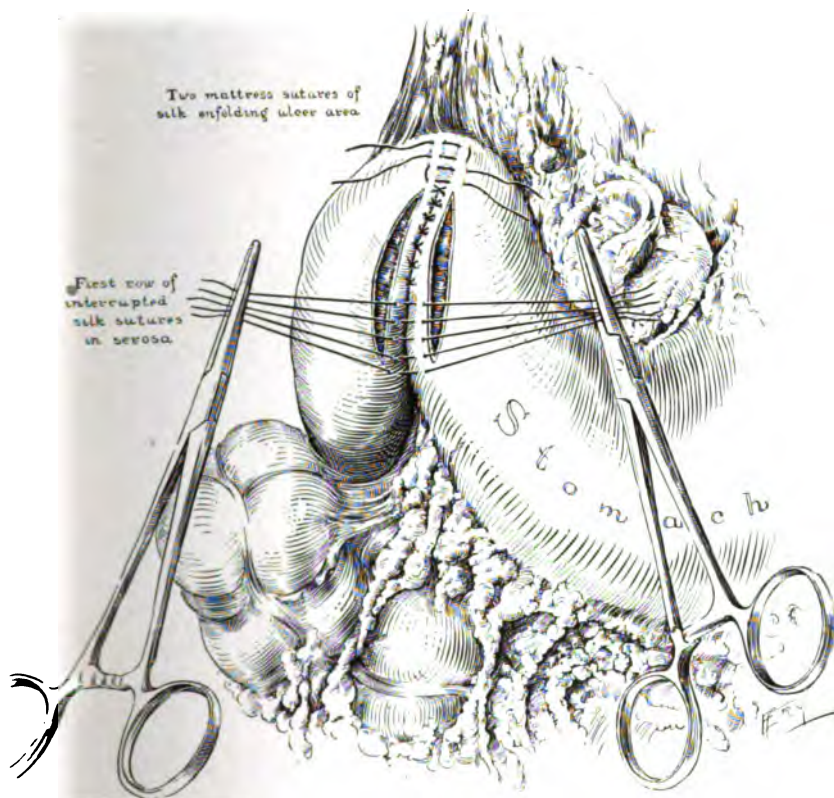
Fig. 20.—Gastroduodenostomy for obstructing ulcer with an angulation.   (See Fig. 19.)

interrupted sutures of fine silk are placed posteriorly, parallel to the
pylorus, and usually immediately in front of the scarred tissues.   A
continuous suture of fine chromic catgut is placed in front of the silk
suture, extending slightly above and slightly below the proposed opening.
The stomach and duodenum are now opened, actively bleeding vessels
separately ligated, and the anastomosis made just as in a gastrojeju-
nostomy with No. 2 chromic catgut (Fig. 21).   The posterior suture
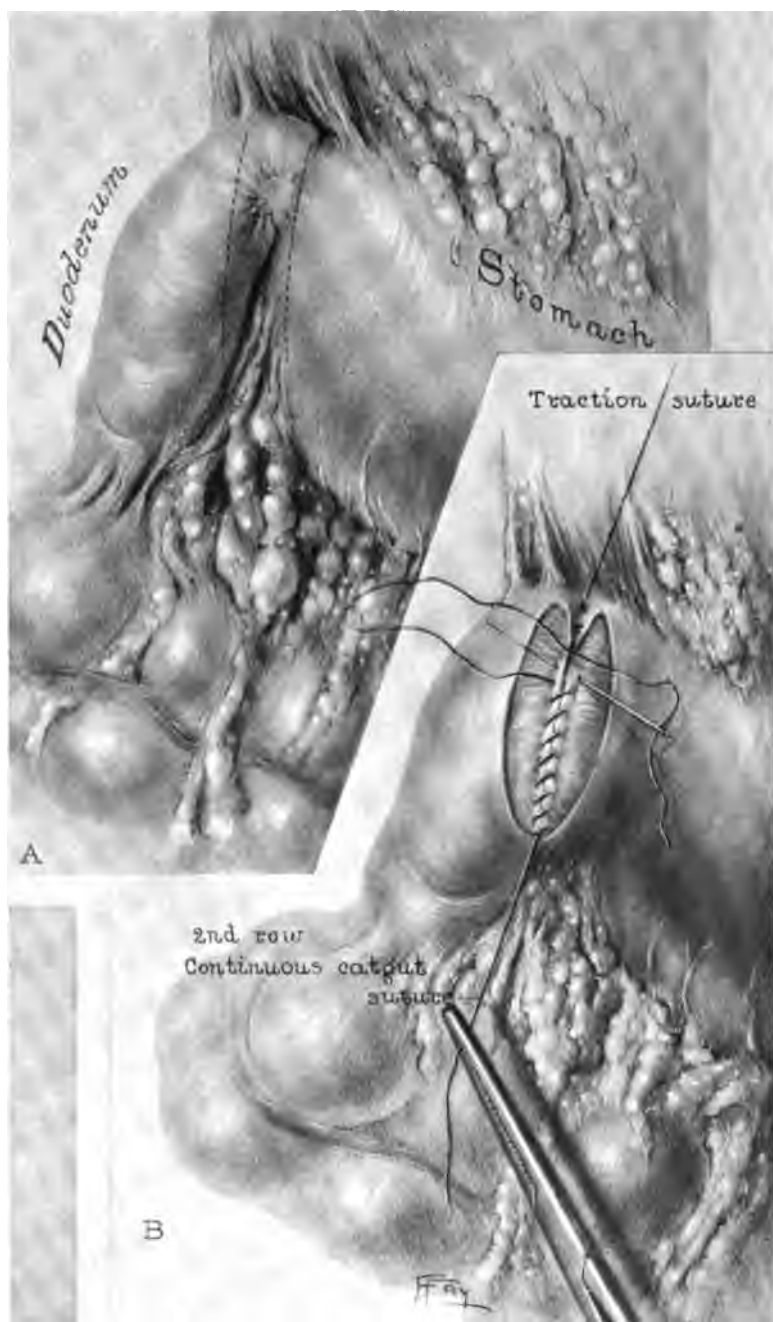
Fig. 21.—A, Easily mobilized duodenopyloric ulcer. Gastroduodenostomy made in front of the ulcer. B, gastroduodenostomy in progress.

lines are now duplicated anteriorly, *i. e.*, a row of fine chromic gut and finally a few interrupted sutures of silk. No clamps are used, but contamination, although not possessing serious possibilities, is largely avoided by careful isolation of the operative field and by suitable wound protection.

The operation, under good circumstances, is easier and can be done in less time than a posterior gastrojejunostomy. In other cases, however (usually when the operation is not one of choice), exposure is difficult on account of the deeply placed and fixed pylorus, but even in these unfavorable cases the results of the operation and its adaptability to specific conditions have been exceedingly satisfactory.

REFERENCES

1. Billroth, T.: Offenes Schreiben an Herrn. Dr. L. Wittelshöfer über die erste mit günstigem Ausgange ausgeführte Pylorektomie. Wien. med. Wchnschr., 1881. Cited by Bier, A., Braun, H., and Kümmell, H.: Chirurgische Operationslehre. Leipzig, Barth, 1912, ii, pp. 383, 405.
2. Finney, J. M. T.: A new method of pyloroplasty. Tr. Am. Surg. Assn., 1902, xx, 165–190. Abst. in Bull. Johns Hopkins Hosp., 1902, xiii, 155–161.
3. Heinecke: Inaug. Dissert., Fürth, 1886. Cited by Finney, loc. cit.
4. Jaboulay, M.: La gastro-enterostomie, la jejunoduodenostomie; la resection du py-lore. Arch. prov. de chir., 1892, i, 1–22. Inconvenients de la gastro-enterostomie simple, et moyens d'y remedier. Province méd., 1894, viii, 61–64.
5. Kocher: The freeing of the duodenum and gastro-duodenostomy. Scottish Med. and Surg. Jour., 1903, xiii, 311–318.
6. Kümmell, K.: Cited by Moynihan, loc. cit.
7. Mikulicz, J.: Zur operativen Behandlung des stenosirenden Magengeschwüres. Ver-handl. d. deutsch. Gesellsch. f. Chir., 1887, xxxviii, 769, 798, 817. Also Arch. f. klin. Chir., 1888, xxxvii, 79–90.
8. Moynihan, B.: Abdominal operations. Ed. 3, Philadelphia, Saunders, 1915, p. 240.
9. Terrier, F.: De las gastro-enterostomie posterieure. xiv Cong. franc. de Chir., Proc.-verb., Paris, 1901, pp. 479–496. Also Rev. de chir., 1902, xxv, 369–410.
10. Villard, E.: De la gastroduodenostomie sous-pylorique. Rev. de chir., 1900, xxiii, 495–520. Also Écho méd. de Lyon, 1900, v, 171–173.

RESTORATION OF GASTRO-INTESTINAL CONTINUITY BY MEANS OF ANTECOLIC GASTRO-JEJUNOSTOMY FOLLOWING PARTIAL GASTRECTOMY FOR CANCER OF THE PYLORIC END OF THE STOMACH*

D. C. BALFOUR

The cure of cancer of the stomach by surgical removal is being accomplished with an increasing frequency, a fact largely due to the progress which has been made in the two most important phases of the subject, viz., diagnosis and treatment.

Prominent factors which have contributed toward more accurate and earlier diagnoses have been: The better appreciation of the clinical history, the x-ray, and the relative values of each, the recognition of the necessity of most thorough investigation of early symptoms, and particularly, of the danger of neglecting the chronic gastric ulcer, and a decreasing pessimism on the part of both the laity and the medical profession in their attitude toward cancer of the stomach.

The surgical treatment of cancer of the stomach has become more efficient, not only because of the foregoing, but because there is a general improvement in surgical technic, a more exact knowledge of the surgical limitations in gastric cancer, and the development of the technical methods employed in gastric resection.

The methods of gastric resection which have been most successful in our clinic during the past decade are:

1. The Billroth No. 2 operation, which gave decidedly better results than any of the preceding methods. It was employed for some years with much satisfaction. This operation of resection and suture posterior gastro-enterostomy was necessarily varied by circumstances, so that anterior gastro-enterostomy and a Murphy-button anastomosis occasionally were indicated and made use of to reëstablish the continuity of the gastro-intestinal tract.

2. About four years ago the so-called Polya operation, which seemed to possess quite obvious advantages over the Billroth No. 2 in a considerable percentage of cases, was adopted in the Clinic. This operation, described by W. J. Mayo in 1915, while followed by better results than the Billroth No. 2, still presented technical difficulties under certain conditions, particularly following extensive gastric resections. In such cases it was sometimes quite impossible to bring the gastric stump with the attached jejunum satisfactorily through and below the level of the opening which had been made in the transverse mesocolon.

3. During the past few months we have employed a method which has given better results than any we have heretofore used, and inasmuch as it has other advantages, we now consider it the best routine operation for the removal of gastric cancer.

The resection is carried out in the ordinary way, with especial attention to such important points as the wide
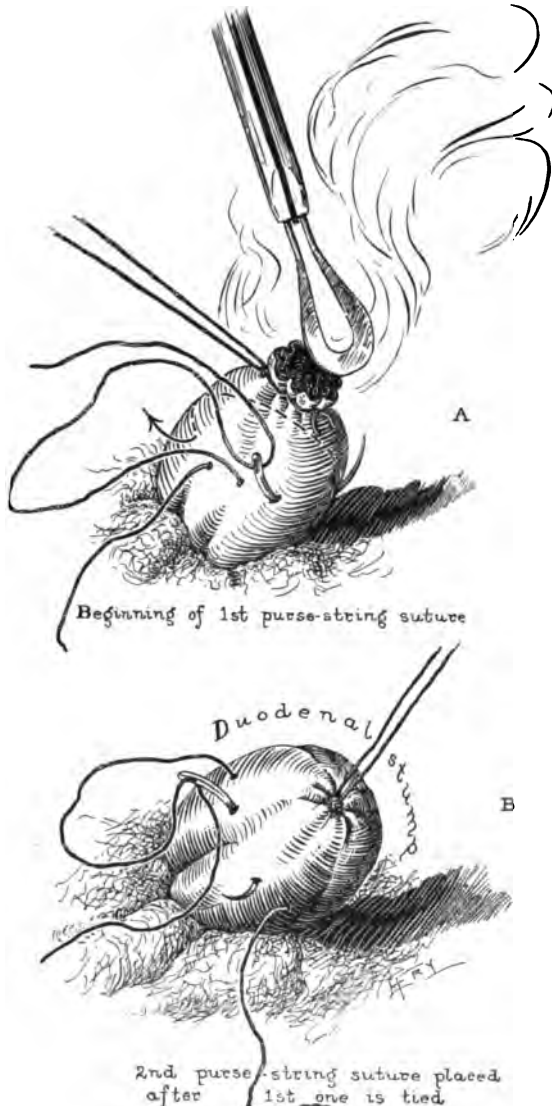
Fig. 22.—A, The end of the duodenum transfixed and tied with catgut. The actual cautery used for sterilizing stump beyond ligature. The purse-string suture in place. B, The stump inverted and first catgut purse-string suture tied. Second catgut purse-string suture in place below the first. A few interrupted silk sutures may be placed to draw together the sheath of the pancreas and omentum in the vicinity, thereby burying the end of the duodenum.

removal of gland-bearing tissue, the avoiding of injury to the middle colic blood supply of the transverse colon, the resection made well

beyond the cancer limits, the cauterization of all cut mucous surfaces to prevent cancer-cell transplantation, and the secure inversion and burial of the duodenal stump. The operative field is inspected and

carefully isolated by fresh packs, and the second stage is carried out as follows (Figs. 22 and 23).

The first loop of jejunum is procured, and a point about 14 to 18 inches from the duodenojejunal angle is marked. The jejunum is then carried up in front of the transverse colon and omentum and a segment of suitable size is chosen at the point already marked. This section of jejunum is lightly grasped with rubber-covered forceps, and directed so that the proximal end of the loop will be approximated to the lesser curvature of the stomach. A series of interrupted silk sutures in the serosa is used for the first line posteriorly, beginning at the greater curvature, All these sutures are placed before any are tied, and the ends of the top and bottom sutures may be conveniently left as guides. The first suture line is about one-half inch below the clamp on the cut-end of the stomach, and on the side of the jejunum about three-fourths of an inch from the summit of the loop. In extensive resections it is extremely important to get the best possible exposure of the lesser curvature, for at this point it is occasionally difficult to make a secure anastomosis, and it is along the lesser curvature that inflammatory products frequently extend, rendering the gastric wall friable and a distinct source of danger. Any measure in such cases which will prevent retraction of the lesser curvature should be utilized. We still find the right-angled rubber-covered clamp of greatest service for this purpose. The jejunum is now incised on the line (Fig. 24) and the crushing clamp removed from the stomach. (If it has been possible at any previous stage in the operation to place without difficulty a straight, rubber-covered clamp at a higher level on the stomach, soiling by unevacuated gastric contents will be prevented.) Any actively bleeding vessels are ligated. The posterior row of the anastomosis uniting the posterior wall of the stomach to the inner cut edge of the jejunum is of chromic catgut. The stitches on the gastric side should be taken after the edge which has been crushed by the clamp has been trimmed with the scissors. A second row of finer catgut may be used to advantage in the posterior line. The first chromic catgut suture is continued in front in the usual way to complete the closure. An interrupted silk suture line similar to that used posteriorly is placed anteriorly, particular care being taken to reinforce the angle of anastomosis at the lesser curvature. A few interrupted silk sutures are placed where necessary further to protect the anterior suture line and the suture at the lesser curvature, the stump of gastrohepatic omentum which contains the ligated gastric artery being utilized as a support to the gastrojejunal angle at this point.

The procedure as described is applicable to the majority of cases (Fig. 25). When, however, chronic pyloric obstruction has greatly
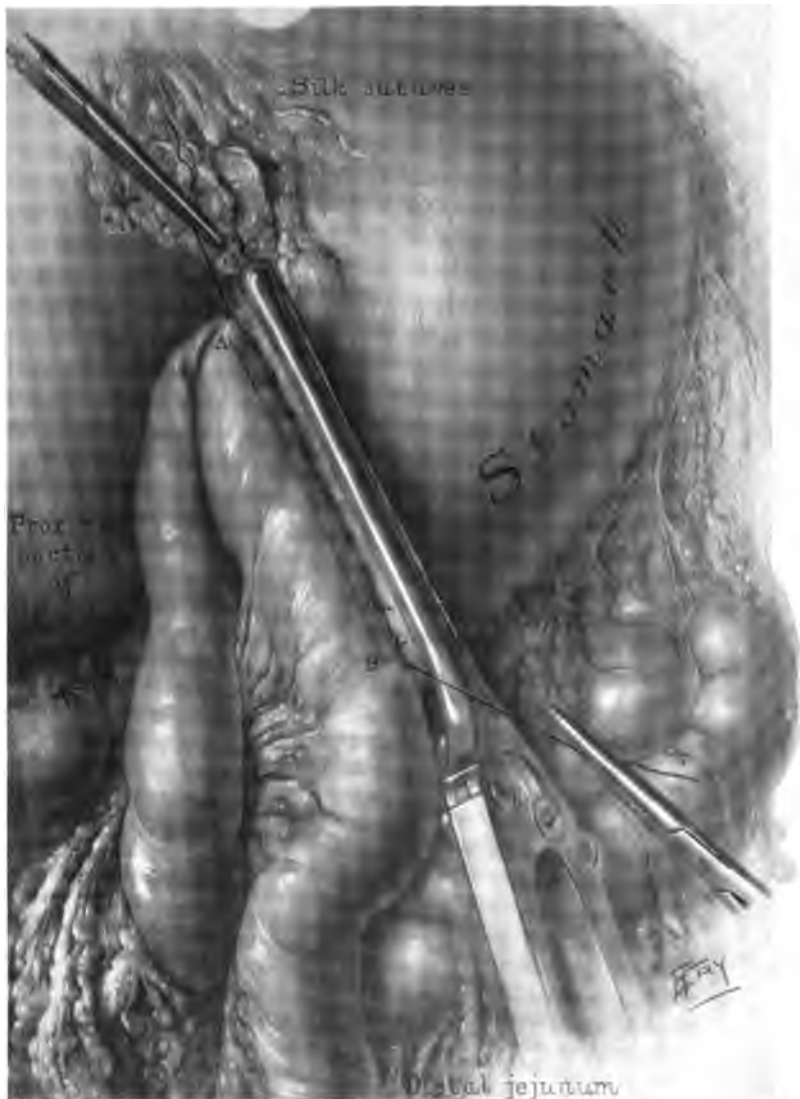

Fig. 24.—First row of interrupted silk sutures uniting the proximal portion of the jejunum to the posterior wall of the stomach. Antecolic. (Balfour.)

dilated the stomach, the gastric outlet after resection is often much larger than is necessary for the anastomosis. Under such circumstances the outlet may be decreased by partly closing it at the upper angle with

sutures, as advised and practised by C. H. Mayo, or the outlet may be approximated to a much smaller opening in the jejunum by suitable suturing. Thus, if the gastric outlet is one-third larger than the size of the opening desired in the jejunum, the intervals between all stitches on the gastric side should be one-third greater than those on the jejunal side. The readiness with which the stomach will adjust itself is, of course, largely dependent on the fact that its great size is abnormal and the stretched-out tissues tend to contract rapidly. However, it has
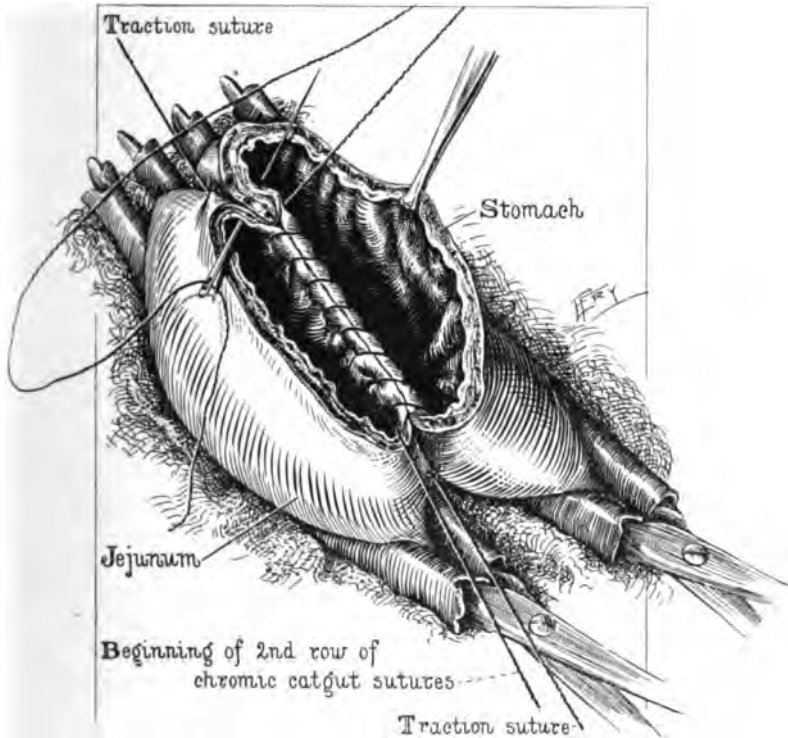
Fig. 25.—Completion of gastrojejunal union by continuous through-and-through suture of chromic catgut.

been our experience that there is no objection to an anastomosis of considerable size (Fig. 26).

The advantages of the antecolic end (gastric) to side (jejunum) method are quite obvious. It has been our experience that it can be used in practically every case, that it is simpler, safer, and can be accomplished in less time than any other method. The operation may be completed well within the hour, and if conditions for operation are favorable, even within half an hour. Its particular advantage is seen,

as I have intimated, in extensive resections, when such a small segment of stomach remains that posterior gastro-enterostomy would be difficult. This fact makes it quite possible that not only will the method result in more radical operations in gastric cancer, but by reason of this advantage it will occasionally permit resection in cases heretofore considered inoper-

Fig. 26.—Position of the anastomosis with relation to the transverse colon on replacement of the viscera after completing operation. Abdominal wound ready for closure.

able. No disadvantages in the method have been encountered and it has been the experience of the surgical staff at the Clinic that patients in whom this method has been employed are less subject to postoperative complications than are those operated on by other methods.

That the operation is of less risk than other methods is very definitely shown by our operative mortality statistics. From January, 1907, to August 16, 1917, in 318 resections by the Billroth No. 2 method, there was an operative mortality of 13.2 per cent; in 104 cases by the Polya method, a mortality of 14.4 per cent, while in 38 cases with the method I have described the mortality was only 5.2 per cent. This comparison of operative mortality is quite fair, inasmuch as the operations were done by the same surgeons in the same clinic with similar surgical indications.*

* The statistics of the operative mortality following the Billroth method No. 1, the Kocher method, and segmental resections in the Clinic are not quoted as they are not comparable.

LEFT PARADUODENAL HERNIA: DESCRIPTION OF ONE CASE*

A. U. DESJARDINS

Several varieties of paraduodenal hernia have been observed and described. Such hernias are of considerable importance to the surgeon, because, although rarely recognized before death or before an operation for the relief of obstructive or strangulation phenomena, they may be encountered in the course of operations undertaken for the treatment of more or less commonplace abdominal disturbances. The majority of cases thus far reported have been discovered during the course of post-mortem examinations of persons having died from causes in no way associated with the hernia. A few cases are on record in which the surgeon, operating for the relief of obstruction or strangulation, found the hernia and successfully dealt with it.

The first real contribution to our understanding of this type of hernia we owe to Treitz, whose work dates back to 1857. Unfortunately, in his description of a fossa which he called "duodenojejunal" he included what is now considered a second fossa, the "paraduodenal" fossa of Landzert. Later Broesike, Gruber, Waldeyer, Landzert, and Jonnesco added greatly to our knowledge of the subject, but in so doing confused it to some extent by describing the same fossæ under different names and different fossæ under the same names, so that to review the literature would be tedious, indeed, were it not for the admirable monograph of Moynihan.

The terms "duodenal" and "duodenojejunal," which have been applied to this type of hernia, are somewhat misleading, and might be thought to imply a displacement of the duodenum into some adventitious sac, but such is not the case; it refers to a hernia of the entire small bowel, or some part of it, into a sac derived from folds of peritoneum and fossæ normally to be found about the terminal, or fourth, portion of the duodenum. For that reason I prefer to use the term "paraduodenal," which is more accurate.

Inasmuch as a clear understanding of this type of retroperitoneal hernia involves a knowledge of the anatomy of various folds and fossæ adjacent to the fourth duodenal segment, these fossæ and their relations will be briefly described.

Paraduodenal Folds and Fossæ

If the great omentum and transverse colon are reflected and pulled upward over the costal arch, and slight traction downward and to the right side is made upon the jejunum, there will be seen passing from the peritoneal surface of the superior, or in some cases of the anterosuperior, aspect of the duodenojejunal angle upward, forward, and to the left side, a thin-edged, peritoneum-covered fold, the lower attachment of which is lost in the peritoneum covering this portion of the gut, the upper attachment blending with the root of the transverse mesocolon adjoining the splenic flexure. This is the ligament of Treitz. Its thin anterior edge is concave upward and slightly toward the right side, and the middle, narrower portion crosses over the inferior mesenteric vein in an oblique direction upward and to the left. In the substance of this fold are involuntary muscle-fibers derived from the left crus of the diaphragm. With the viscera in situ this fold cannot be made out, and traction upward on the colon and downward and to the right on the jejunum is necessary to bring it out.

With the colon reflected and the small bowel pulled over to the right as described, there appear in most bodies, immediately to the left of the fourth portion of the duodenum, one or more fossæ bounded by definite folds of peritoneum. Jonnesco describes in his work five fossæ. Moynihan describes nine, four of which, however, he considers of little importance.

The fossæ most frequently encountered in a consecutive examination of 100 bodies, ranging in age from birth to seventy-five years, are, in order of frequency:

1. Inferior paraduodenal fossa of Treitz................ 60 per cent
2. Combined superior and inferior paraduodenal fossæ.... 30 per cent
3. Superior paraduodenal fossa........................ 5 per cent
4. Paraduodenal fossa of Landzert.................... 2 per cent
5. Duodenojejunal or mesocolic fossa................. 2 per cent
6. Fossa of Waldeyer................................ 1 per cent

I have not been able to study these fossæ in the embryo, at which time they are said to be more frequent.

The superior paraduodenal fossa.—Below the ligament of Treitz, on

a plane posterior to it, immediately to the left of the duodenojejunal
angle, there can be seen in many bodies a thin, sometimes almost trans-
parent, fold of peritoneum extending from the peritoneal surface of the
terminal portion of the duodenum toward the left, a distance of from
1 to 2 cm. This fold is, in a general way, triangular in shape, and is
bounded below by a thin, semilunar margin, the concavity of which is
directed downward and to the left. This fold forms the anterior boun-

Fig. 27.—The superior and inferior paraduodenal folds and fossa, and the submesenteric fossa (Landzert).

dary of a triangular fossa, usually from 1 to 2 cm. deep, the apex of
which is directed upward or upward and slightly to the right, and is in
close relation to the pancreas. The fossa is bounded on the right by the
terminal portion of the duodenum, and on the left by the line of fusion
between the fold and the posterior parietal peritoneum, just to the right
of the inferior mesenteric vein, which courses in a gentle curve along the
left side of the fossa (Fig. 27). This has been called by different writers

the duodenal, duodenojejunal, or the superior duodenal fossa, but inasmuch as all these fossæ are paraduodenal, I shall call it the superior paraduodenal fossa.

The inferior paraduodenal fossa of Treitz.—A short distance below the orifice of this superior fossa there is still more frequently another fossa, bounded anteriorly by a reflection from the peritoneal investment of the fourth portion of the duodenum, posteriorly by the posterior parietal peritoneum, on the right side by the duodenum, and on the left by the line of fusion between the fold and the parietal peritoneum. The upper margin of this fold is semilunar, with its concavity directed upward or
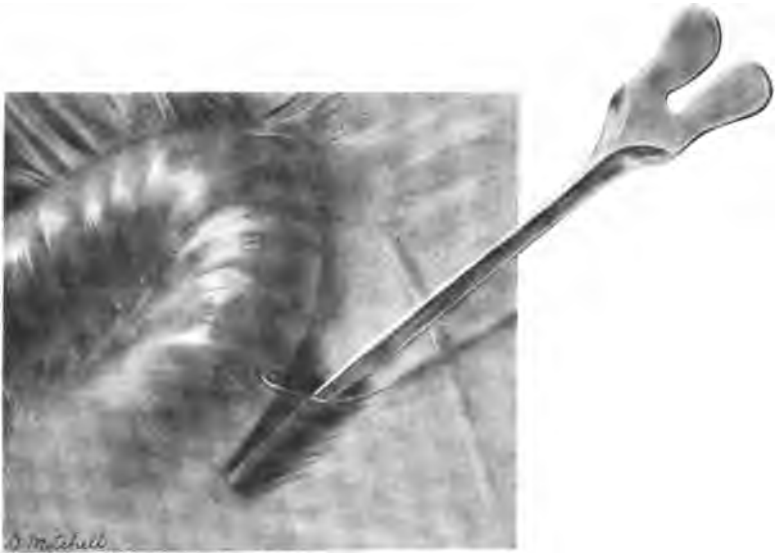
Fig. 28.—Inferior paraduodenal fossa (Treitz); director inserted into the fossa.

upward and slightly to the left, and forms the anterior margin of the opening of a fossa of variable depth, the apex or bottom of which is directed downward and to the right, immediately adjoining the fourth portion of the duodenum (Fig. 28). This is the inferior paraduodenal fossa, and corresponds to the fossa described by Treitz, and named by him "duodenojejunal." Moynihan describes it as the inferior duodenal fossa.

The exact position and depth of this fossa vary more or less. In three instances I was able to introduce my little finger into the fossa to a depth of 5 cm. Its usual position is along the left edge of the body of

the third lumbar vertebra. In many bodies the superior and inferior fossæ coexist, and in one case the left ends of the folds forming the anterior boundary of the orifices of both fossæ had become fused into one, resulting in a common opening for both fossæ (Fig. 29).

At a variable distance below the apex of the inferior fossa the left colic artery, coursing upward and to the left, crosses the inferior mesenteric vein, the two vessels constituting the *vascular arch of Treitz*. This
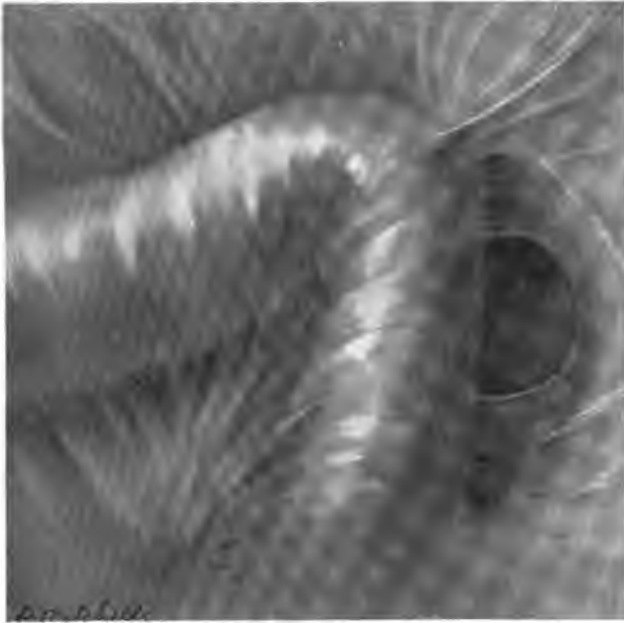
Fig. 29.—Superior and inferior paraduodenal fossæ with left ends of folds fused to form a common orifice for both fossæ.

arch is of fundamental importance because the relations of these vessels to the neck of a hernia in this region determine its variety.

The paraduodenal fossa of Landzert.—The paraduodenal fossa of Landzert is produced by a dipping of the posterior parietal peritoneum around the right side of and behind the inferior mesenteric vein as it curves downward a short distance to the left of the fourth duodenal segment. This dipping of the peritoneum about the vein gives to the vessel a mesentery, so to speak, the vein arching to the left and then downward in the edge of the fold, the fossa being beneath or posterior to it (Fig. 30). This fossa is of great importance because it is that in which most of the

paraduodenal herniæ reported have occurred, as determined by the relations of the inferior mesenteric vein and left colic artery to the neck of the sac.   The extent of the fossa of Landzert varies considerably and its exact boundaries are not easy to determine because, as pointed out by Moynihan, "it exists not seldom in conjunction with other fossæ. The complications are almost as frequent as the normal." When such a complication occurs it is most frequently in the form of an associated superior paraduodenal fossa.

Fig. 30.—Paraduodenal fossa of Landzert, showing the inferior mesenteric vein running downward in the edge of the fold.

The paraduodenojejunal fossa.—The duodenojejunal fossa, identical with the *fossette duodéno-jéjunale ou mésocolique* of Jonnesco, is the only one of the paraduodenal fossæ, which have been miscalled duodenojejunal, to really deserve the name. In the cases in which the fossa is encountered the duodenojejunal angle is buried in the root of the transverse mesocolon, the anterior leaf of which extends farther down over the anterosuperior aspect of the duodenojejunal angle, where it fuses with the peritoneal investment of this portion of the gut. In this anterior leaf of the mesocolon, just above the line of fusion, there may be seen

an arched opening, in some cases so flattened against the bowel-wall as
to require the introduction of a probe in order to demonstrate the fossa.
The direction of the cavity is upward and to the left, the bottom of the
fossa being in close relation to the pancreas and inferior mesenteric vein
(Fig. 31). Jonnesco describes a similar fossa with a double opening which
is merely a modification. This duodenal fossa is to be found in from 5
to 10 per cent of bodies examined.

The mesocolic fossa.—The fossa described under this name by Moy-
nihan is quite uncommon, but it is of some importance as the possible
origin of a hernia. It is located at some distance from the ascending
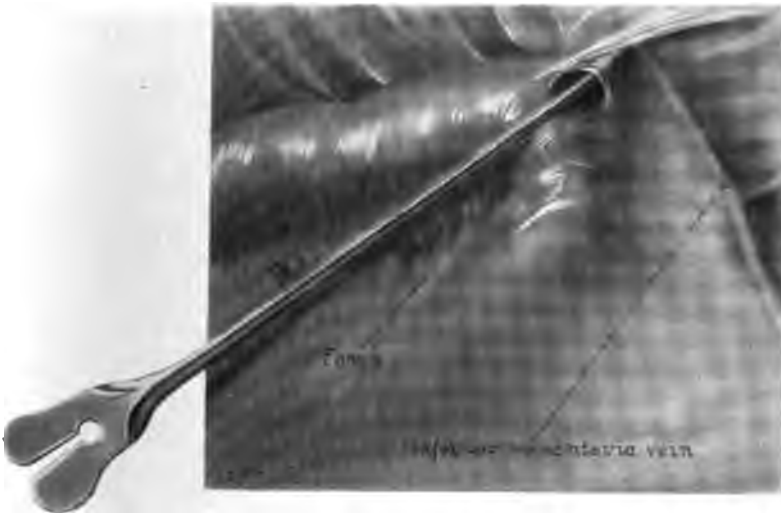
Fig. 31.—Mesocolic type of fossa with duodenojejunal angle buried in the transverse mesocolon.

fourth portion of the duodenum, to the left of the inferior mesenteric
vein, and extends to the left between the leaves of the mesocolon in the
region of the splenic flexure. A branch of the left colic artery runs up-
ward in the fold forming the anterior boundary of the fossa.

The paraduodenal fossa of Waldeyer.—Waldeyer, in 1874, described
a fossa in the mesojejunum, beneath the superior mesenteric artery and
immediately below the duodenum, which he called "mesenterico-parie-
tal" and which Moynihan considers of more frequent occurrence than
some of the other fossæ described in his work. In 100 bodies examined I
have seen it but once, and although the relations of this fossa were those
mentioned, I am inclined to consider it as a variation from the more

common inferior fossa of Treitz. I have seen a number of low fossæ of Treitz, the bottom or apex of which was in intimate relation to the beginning of the fourth portion of the duodenum, and it does not require a considerable stretching of the imagination to associate the fossa of Waldeyer with a low inferior paraduodenal fossa of Treitz. Moynihan's description is as follows: "The fossa has its orifice to the left, its blind extremity to the right and downward. In front it is bounded by the superior mesenteric artery and behind by the lumbar vertebræ. The peritoneum of the left leaf of the mesentery lines the fossa, that of the right covers the blind end, and is then continued directly into the posterior parietal peritoneum." It is in this fossa that a right paraduodenal hernia occurs, and since we are dealing only with the left type of hernia it will not be referred to again.

Three other fossæ have been described, but they are so rare and of so little importance that they need not be considered.

Origin of Paraduodenal Folds and Fossæ

Several explanations of the origin of these folds and fossæ have been advanced. The first interpretation was that of Treitz, who considered them to be due to the movement of the intestine associated with its embryonic development. During the early stage of its development the intestinal tract consists of a fairly simple and straight tube attached to the midline of the body by a fold of peritoneum. As it grows the stomach becomes differentiated by a dilatation of the tube, and the tube below this gastric dilatation increases in length. Associated with this development is a movement of the stomach from its original longitudinal position with its surfaces looking to right and left, to a transverse position, the original right surface of the stomach becoming posterior and its former left surface the anterior. As this movement, with which the duodenum is associated, takes place, there is a gradual fusion of the peritoneum about these structures. Treitz's view was that the increasing length and consequent dragging of the intestine exerting traction on the fixed duodenum and mesocolic root were responsible for these folds, and that the fossæ were the result of these "traction" folds. This view is now quite untenable.

Waldeyer's theory was based on the relation of the inferior mesenteric vein to the neck of the sac. He thought that, in the course of development of the posterior parietal peritoneum, the vein raised a fold forming a fossa, and for that reason he considered the fold as vascular in

origin. This view cannot be accepted because there are several folds and fossæ which have no such vascular relationships.

The logical explanation, which covers the embryologic and anatomic requirements, is that of Moynihan, who looks on them as "fusion folds between the original left, afterward anterior, surface of the ascending portion of the duodenum and the right, or anterior surface of the descending mesocolon folds, which date their origin from the time when these two peritoneal surfaces are in close. apposition." This interpretation makes it possible to understand the frequent occurrence of atypical fossæ.

Factors Involved in the Production of Hernia

Treitz has formulated three postulates as indispensable for the occurrence of a left duodenal hernia:

1. The presence of a fossa.

2. The presence in the neck of the sac of the inferior mesenteric vein.

3. Sufficient mobility of the small bowel to allow it to pass into the sac derived from this fossa.

However, it would seem that, beside these factors, there would be required an increased intra-abdominal pressure sufficient to initiate the hernia, because the natural drag of the intestine is away from these fossæ, the opening of which is seldom large. It is conceivable that in some cases the hernia may be congenital, having been produced as a result of increased intra-abdominal tension either before or during parturition.

The second postulate may or may not be fulfilled, depending on whether or not the hernia is one into the paraduodenal fossa of Landzert, because this is the only fossa with which the vein is in such close relation.

Report of a Case

Case 193232 is that of a man fifty-six years of age, who came to the Mayo Clinic May 4, 1917, seeking relief for shortness of breath and abdominal distention. Physical examination revealed an enlargement of the right lobe of the thyroid, multiple firm, nodular masses in the upper abdomen, an enlarged, palpable spleen, and a large quantity of fluid in the left pleural cavity causing a considerable displacement of the heart to the right. On the same day a supraclavicular gland was removed for microscopic examination and proved to be lymphosarcomatous. I merely mention these facts without dwelling on them because they have no bearing on the hernia, except to show that the patient had never had any symptoms that might lead one to suspect the presence of an ab-

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dominal condition, in no way responsible for his death, which occurred on May 8.

At the necropsy, performed fifteen hours after death, the following pertinent lesions were named as the lethal factors in the anatomic diagnosis: Marked general lymphosarcomatosis; chronic nephritis; cardiac hypertrophy and bilateral hemohydrothorax.

The following is a transcript of the description of the hernia made at the time:

"On opening the abdominal cavity the small intestine appears as in the early stage of a plastic peritonitis. The coils seem slightly adherent and hyperemic, but it is strikingly noteworthy that the intestinal mass has a sharply ovoid shape, smooth and uniformly rounded, occupying the center of the abdominal cavity with the colon, forming a frame about it, as shown in Figure 32. On attempting to separate some of the coils, however, it is at once apparent that the bowel is covered by a thin, transparent membrane in which vessels can be seen coursing from above downward and from below upward. The mass is about the size of a human head looked at from above; it measures over all 20 cm. in its longitudinal diameter and 17 cm. in the transverse. There is an interval of 5 cm. between the lower pole of the mass and the symphysis pubis. Recognizing a hernial sac and seeking its orifice, I find it above and behind the lower pole and to the right of the middle line, in the form of a long, oblique opening, slightly semilunar, with its concavity pointing downward and to the right. The anterior margin of the neck of the sac is thick and cord-like, and passes upward and to the right to the space between the sac and the ascending colon, where it becomes lost in the retroperitoneal tissues, among masses of enlarged glands. At the left and inferior end of the opening the cord-like anterior margin of the neck curves upward and to the left to blend with the descending mesocolon. Four fingers can be readily introduced into this orifice up to the metacarpophalangeal joints. Traction on the lower pole upward and to the left brings the orifice into view, and it is seen that the entire small bowel, with the exception of the terminal five inches of ileum, is inside the hernial sac. There are no adhesions between the bowel and the sac.

"The normal anatomic relations are so distorted by the enormous enlargement of all the retroperitoneal lymph-glands that, in order to determine the variety of this hernia, it is necessary to work out the relations of the inferior mesenteric vein and left colic artery to the sac. The inferior mesenteric vein passes beneath the posterior parietal peritoneum, across the back of the hernial sac, to the space between it and the ascending colon on the right side. Then, coursing downward and inward to the right margin of the hernial orifice, it passes from right to left in the thickened anterior margin, forming the anterior boundary of the neck to the left side.

"The left colic artery runs toward the left side, where, after coursing downward in the space between the sac and the descending colon, it

enters the left side of the anterior margin of the hernial orifice and passes through it upward and to the right side. From both vessels as they pass
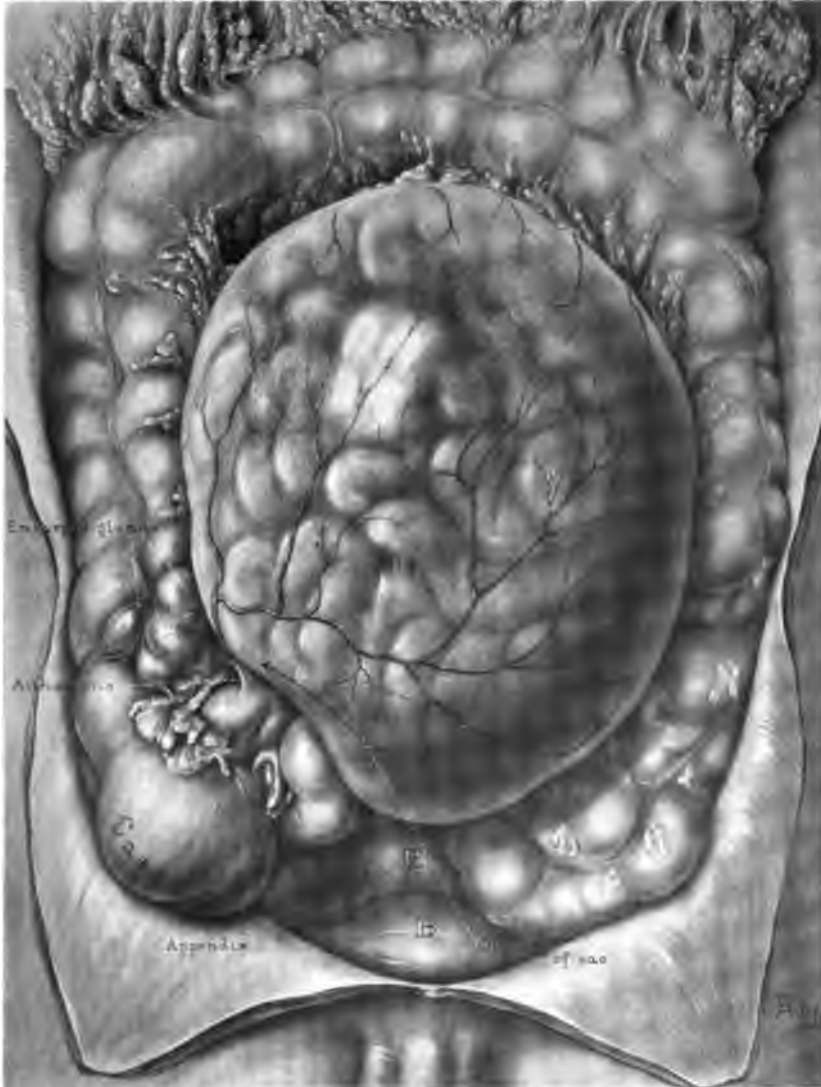

Fig. 32.—Left paraduodenal hernia as seen at autopsy. The sac contains the entire small bowel, except the terminal five inches.

through the thickened band, forming the anterior margin of the neck of the sac, branches pass upward between the two fused layers of the sac

itself. Similar branches pass downward from the middle and left colic vessels, running in the space between the sac and the transverse and descending colon."

The accompanying diagram (Fig. 33) gives a better idea of these relations. This, then, is a hernia into the paraduodenal fossa of Landzert, and is to be classified as a left paraduodenal hernia.
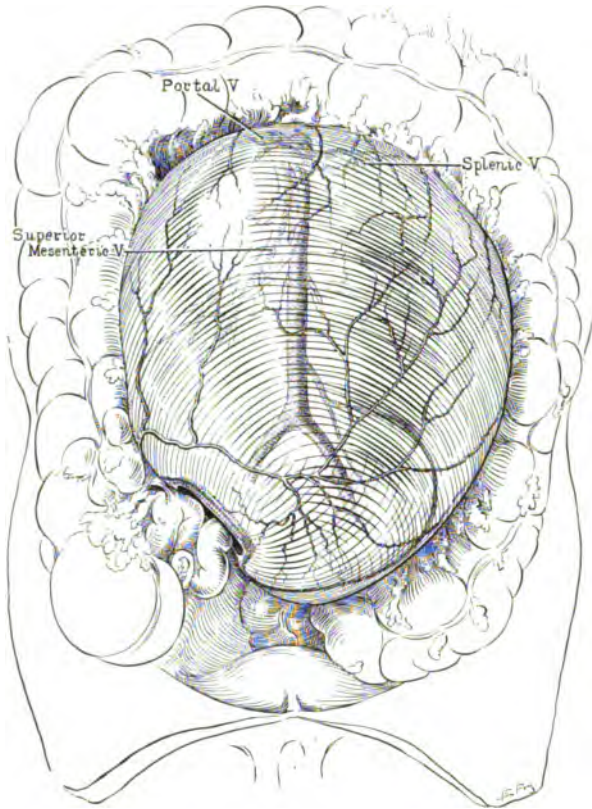
Fig. 33.—Diagram showing the relations of the inferior mesenteric vein and left colic artery to the hernial sac.

In his monograph, published in 1906, Moynihan gives a list of 65 cases reported up to that time. Since then Short has collected 17 more cases, one of which, however, had already been reported by Moynihan, making, up to 1914, a total of 81. Of the 16 cases collected and listed by Short, 7 patients were operated on and recovered. One of these cases, that of Heller, was a complete hernia, very similar to my own.

Since the beginning of 1914 I have been able to gather the four following cases:

1914. Davis, L.: A case of strangulated retroperitoneal hernia of the small intestine into the paraduodenal fossa. Boston Med. and Surg. Jour., 1914, clxx, 272–274.
1914. Pybus, F. C.: Symptoms of acute intestinal obstruction operated and cured. Brit. Med. Jour., 1914, ii, 14.
1914. Nuzum, F., and Nuzum, J.: Two unusual internal hernias—one intersigmoid, the other into the paraduodenal pouch of Landzert. Tr. Chicago Path. Soc., 1914, ix, 191.
1916. Pringle. J. H.: Report of a case of hernia into the paraduodenal fossa. Glasgow Med. Jour., 1916, lxxxvi, 65–72.

REFERENCES

1. Broesike, G.: Über intraabdominelle Hernien und Bauchfelltaschen. Berlin, 1891.
2. Gruber, W.: Über die Hernia interna mesogastrica. St. Petersburg. med. Ztschr., 1861, i, 217–258; 1862, ii, 161–167; 1862, iii, 300–303.
3. Heller, E.: Über eine operative geheilte Hernia duodenojejunalis Treitzii. Arch. f. klinische Chir., 1909, xc, 361–366.
4. Jonnesco: Sur l'anatomie topographique du duodénum. Progrès méd., 2 s., ix, 176, 192, 216, 233, 257, 271, 288.
5. Landzert, T.: Über die Hernia retroperitonealis und ihre Beziehungen zur Fossa duodenojejunalis. St. Petersburg. med. Ztschr., 1871, ii, 306–350.
6. Moynihan, B. G. A.: Retro-peritoneal hernia. Lond., Baillière, 1906, 195.
7. Poisson, F.: Les fossettes péri-duodénales et leur role dans la pathogénie des hernies rétropéritonéales. Paris, Lille, 1895, 144 pp.
8. Short, A. R.: A case of retroperitoneal hernia cured by operation, with a report on the literature of the subject. Brit. Jour. Surg., 1915–16, iii, 48–54.
9. Treitz, W.: Hernia retroperitonealis. Ein Beitrag zur Geschichte innerer Hernien. Prag, Credner, 1857, 150 pp.

ENTEROSTOMY AND THE USE OF THE OMENTUM IN THE PREVENTION AND HEALING OF FISTULA*

C. H. MAYO

The operation of enterostomy is a life-saving procedure the necessity for which may be discussed a few hours longer than that of making a tracheotomy. When indicated, it is just as much an operation of necessity or emergency as the latter. Both procedures have indications and marked limitations for obstruction, which is mainly mechanical.

Obstruction of the bowels may result from the toxemia of disease, either local or general, or from adhesions or paresis due to acute or chronic local or diffuse abdominal inflammation. A loop of bowel may become caught beneath a peritoneal band formed from some old infection long since healed. Conditions resembling intestinal obstruction may occur from reflex causes secondary to acute diseases of the kidney.

In the large majority of cases the intestinal obstruction for which the operation of enterostomy is indicated occurs during the first few days following an abdominal operation. The obstruction may be in the large or the small bowel; when in the large bowel a longer time is given for discussion as to its cause and method of treatment; the danger from toxemia is not as serious as in obstruction of the small bowel. In colonic obstruction the danger is from exhaustion or peritonitis resulting from perforation. Visible peristalsis extending irregularly over the abdomen is often noted. Such peristaltic waves are less noticeable in obstruction of the small bowel unless the obstruction is low in the ileum, and is incomplete and chronic. The danger of colonic obstruction following operation is greater when the operation has necessitated any suturing of the bowel. The lower the injury in the intestine, the greater the danger of infection from the suturing of the bowel because of the difference in the type of bacteria commonly found in varying portions of the intestine.

In the small intestine there is the added toxemia of retained secretions and ferments which are delivered to the blood through the lymphatics without the protective influence of the liver which is exerted over the absorbed secretions of the colon (Draper).

In certain abdominal operations involving suturing of the middle or left colon an appendicostomy may be made as a safety-valve to take strains off the suture line, or a small tube may be passed into the rectum, high in the sigmoid, and left there during the first few days following the operation.

After abdominal operations there is usually stasis of peristalsis during the first twenty-four hours. This follows the injury of the peritoneum and is a protective measure occurring after the perforation of ulcers, gunshot wounds, or other abdominal injury, and giving time for the formation of life-saving adhesions.

In children, abdominal operations are performed chiefly for one definite purpose, and exploration is rarely indicated. In adults, the diagnosis of the essential lesion may be most accurate, yet complications of other disease may be present. It is, therefore, best in most cases other than acute infections to explore for associated disease, even though such examinations may be the cause of additional gas colic and stasis following operation. A patient who has had an abdominal operation will probably have some stasis the same day and it should not occasion worry if the condition persists until the next night, even though it may be the cause of considerable pain. Various enemas are given the day after the operation, usually with complete relief. If the patient is not relieved, lavage, laxatives, different kinds of enemas, hypodermic injections of pituitrin or eserin, are given during the second night and third day. If these do not bring relief, it may be concluded that the obstruction is complete. The patient vomits and is toxic from the small bowel secretion. The evening of the third day or the morning of the fourth he is taken to the operating room, the sutures are removed, the incision opened, and the abdomen inspected. When there is general peritonitis, the intestines are red and inflamed or lymph-covered. In such cases an enterostomy is made without exploration. If there is no evidence of general peritonitis, the hand is inserted and passed to the site of the operation, which, in acute or chronic abdominal sepsis, is usually in the pelvic or right iliac region. In the search for obstruction at this early stage the adhesion causing the condition readily gives way and the gurgling of moving gas is felt and heard. When this occurs, enterostomy is not re-

quired. If operation is delayed until late in the fourth day, or even later, there may be toxic paresis as well. In some cases local abscesses are formed, but practically all patients who survive usually recover from the obstruction spontaneously with natural movements eight days from the day of its occurrence, life having been saved by the safety-vent. Patients with obstruction beginning some days following operation usually present the same symptoms at the same period from the day the obstruction began. In such cases bands of adhesions are the principal factor.

Enterostomy is less favorable for diffuse peritonitis than for localized obstruction. In the colon, obstruction is relieved by appendicostomy, cecostomy, colostomy, or the Brown operation of ileostomy. There is rarely spontaneous recovery from obstruction of the large bowel, a second operation being required for permanent relief and the restoration of the anal function.

TECHNIC.—In early operation reopening of the incision is preferable. The advantage of this is that little or no anæsthetic is required for the whole procedure. In late operation a second incision is occasionally advisable. A low-lying loop of distended bowel is elevated into the incision. A segment is freed of gases or fluids and controlled by rubber-covered forceps applied above and below the point selected for perforation. At a point opposite the mesentery a purse-string suture of silk is applied in a diameter of half an inch. The bowel is perforated in the center of the purse-string by a knife, or the perforation may be made by the method of J. W. Long, using the Paquelin or an electric cautery. A catheter, size 10 or 12, is inserted several inches into the intestine and held in place, after the purse-string is tied, by perforating its side with the same needle and tying it into place. This suture will hold for a few days only. It will then cut out of the tissues and may be removed with the catheter when the latter is withdrawn. Two successive purse-string sutures may be applied by the Stamm-Kader method, but the procedure most satisfactory is that of Witzel, i. e., depressing the catheter into the wall of the bowel and suturing together the folds thus formed over the catheter for a space of an inch and a quarter. When the operation is made as a jejunostomy for feeding or for intestinal obstruction in children, the Coffey method of incising the peritoneal and muscular layers of the bowel at the point of depressing the catheter into its wall conserves the lumen of the gut, the tube being placed between the mucosa and the wall of the intestine, and the peritoneum and muscle being approximated over the catheter. This method is rarely followed by a fistula. For

additional security and also to favor closure of the opening, we have passed the catheter through the perforated omentum (Fig. 34) and then
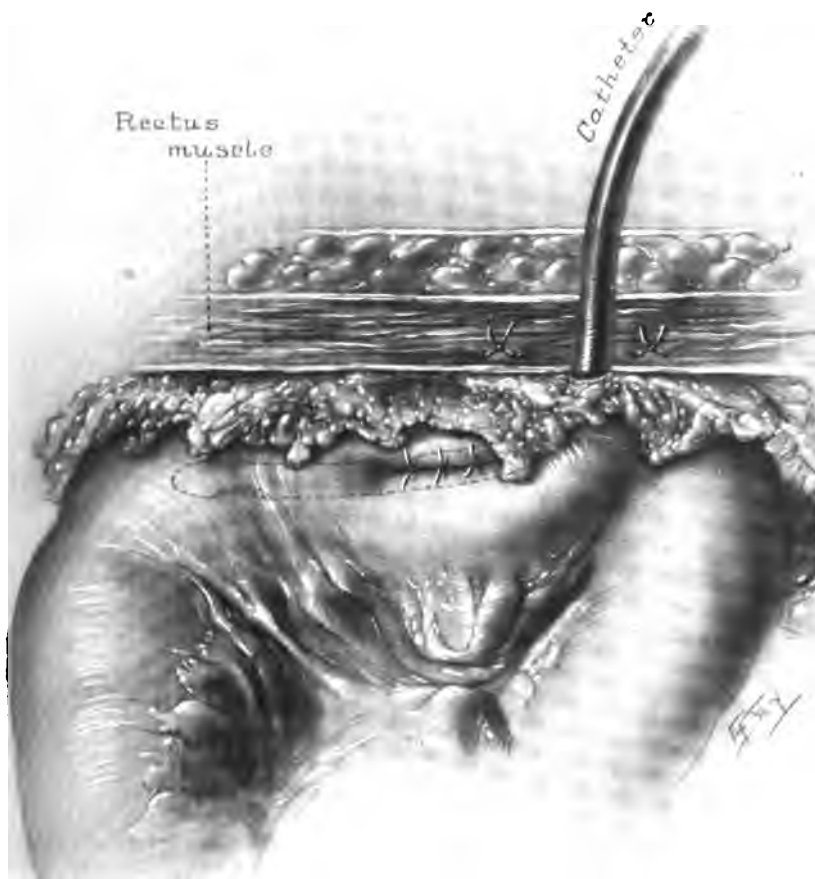

Fig. 34.—Tube passing through the abdominal incision and the omentum and into the lumen of the bowel.

for fixation have included the parietal peritoneum, the omentum, and the intestine in three sutures. This method maintains a movable, even

if adherent, intestine, and the omental graft aids in closing the bowel opening by granulation.

Two unfortunate conditions may occur: (1) The loop of bowel chosen for the opening may be high in the jejunum, leaving but a limited length for nutrition. In this case rectal feeding (intravenous or subcutaneous infusions of saline) will aid until the adhesions subside and relief is obtained. (2) A fistula may occur at the point of enterostomy when it is made without the protection of the omentum. Should a fistula occur, it may be blocked by inserting through it into the intestine an oblong button held by threads in the eyes or through a perforation in the obturator which hold it up against the wall of the bowel at the point of leakage; the threads are then passed through the perforations of a flat button on the skin side of the fistula. This method makes a closure until granulations fill the opening, when the thread can be cut and the inner button passes with the intestinal contents (Dowd, Pallister).

REFERENCES

1. Brown, J. Y.: The superiority of the right side anus in the handling of partial and complete obstruction of the lower colon and sigmoid in cases unsuited for radical operation. Jour. Am. Med. Assn., 1916, lxvii, 486–487.
2. Dowd, C. N.: Enterostomy for ileus. (With Pallister.) Ann. Surg., 1917, lxv, 95–104.
3. Draper, J. W.: Death in acute intestinal obstruction and kindred conditions is due to physiologic disturbance. Jour. Am. Med. Assn., 1910, liv, 5–9.
4. Draper, J. W.: Studies in intestinal obstruction with a report of feeding heterologous jejunal and ileac cells to a human being. Jour. Am. Med. Assn., 1914, lxiii, 1079–1082.
5. Long, J. W.: Enterostomy: A perfected technic. Jour. Am. Med. Assn., 1917, lxviii, 833–835.

JEJUNOSTOMY, ITS INDICATIONS AND METHODS*

C. H. MAYO

Jejunostomy is an operation which, fortunately, is rarely required, but when indicated, it is to be classified among the life-saving, or at least the most important, palliative surgical procedures. The term jejunostomy is often applied when, in making an enterostomy to relieve obstruction, the small intestine is opened. Enterostomy would be the more correct term, as the opening is made in a distended loop of small intestine, very often regardless of whether it is jejunum or ileum. On the other hand, when enterostomy is made for purposes of nutrition, the jejunum is chosen and the opening is made in its first loop.

In cases of obstruction of the small bowel (the so-called ileus) following operation, enterostomy should be done as soon as the evening of the third day or on the fourth day following its inception. The fifth day may be too late. Such obstruction may occur directly after an abdominal operation, or several days later following an apparently normal primary convalescence. Nearly all the cases seen are those which follow operation or are acute obstruction from some unknown cause, and when the enterostomy is made, the patient is usually too seriously ill to warrant prolonged or extensive exploration.

Handley has suggested a jejunal colostomy in such cases. This is an extra procedure on very sick patients, and makes a permanent enterocolostomy, which is only occasionally necessary, a temporary vent being sufficient. It is often difficult to determine whether a high or low opening is made in the bowel, and such a high communication with the colon would possibly develop later trouble.

When the operation is done as an enterostomy for obstruction, it is supplemented by rectal feeding of glucose and fluids. The stomach is also washed every six to eight hours until it is found clear. The opera-

tion is most effective when the obstruction is due to local peritonitis, in which case the local condition will persist for approximately a full week. When the obstruction is from diffuse peritonitis, the operation is less effective but well worth making, as, with the gastric lavage and drainage, some patients may be tided through the temporary period of paretic obstruction and relieved from the toxemia of retained and absorbed intestinal fluids.

Jejunostomy for purposes of nutrition would be indicated with widespread cancer of the stomach obstructing the cardia, and leaving but little room in its contracted and cancer-involved wall for gastrostomy. Patients in this condition are half starved, there is often extreme exhaustion, and it may be impossible or inadvisable to make an extensive preliminary x-ray examination. Gastrostomy in such instances adds to the patient's pain; on the other hand, a jejunostomy will rest the stomach and give immediate relief. We have seen patients gain from 10 to 30 pounds following jejunostomy, and, with complete rest of the stomach, the cancer made slower progress. The operation is advisable in case of extensive laceration of a cancer of the stomach made accidentally during an exploratory examination. Mayo-Robson advises it also in linitis plastica and in extreme cases of vomiting of pregnancy. The operation is so easily and quickly done that we sometimes wonder it is not more commonly chosen in cases of nervous vomiting of girls of from eighteen to twenty-five years of age, instead of the stages of operative procedure, such as the removal of an ovary, then an appendix, then the fixation of a movable kidney, drainage of the gallbladder, and, finally, a gastro-enterostomy, as so often is done in a series.

The operation for purposes of nutrition is performed through a midline or left lateral incision, the upper loop of jejunum being found beneath the transverse colon and the omentum. When the operation is for the relief of obstruction, it is best to reopen the former incision unless it is infected. If there is no general peritonitis and the obstructive condition is recognized early, the patient will not be in extremis and the operator may explore the region of the primary operation. Not infrequently adhesion-bands or kinks may be separated, at once reducing fluids and gases which pass along the bowel with audible gurgling. The enterostomy will not then be necessary. If enterostomy is considered necessary, a distended loop of bowel is stripped of fluids for a few inches and rubber clamps are adjusted to keep the loop empty. The bowel is perforated opposite its mesentery, and a No. 10 English catheter is

inserted a few inches into the lumen of the gut. A purse-string suture adjusts the bowel to the catheter, and the needle passed through its side fixes it in position. The suture may be chromic catgut or silk; if the latter, it comes out with the catheter. The catheter is depressed into the wall of the bowel, and its folds are sutured over the tube for an inch and a half, and a perforation is made in the adjacent omentum and the
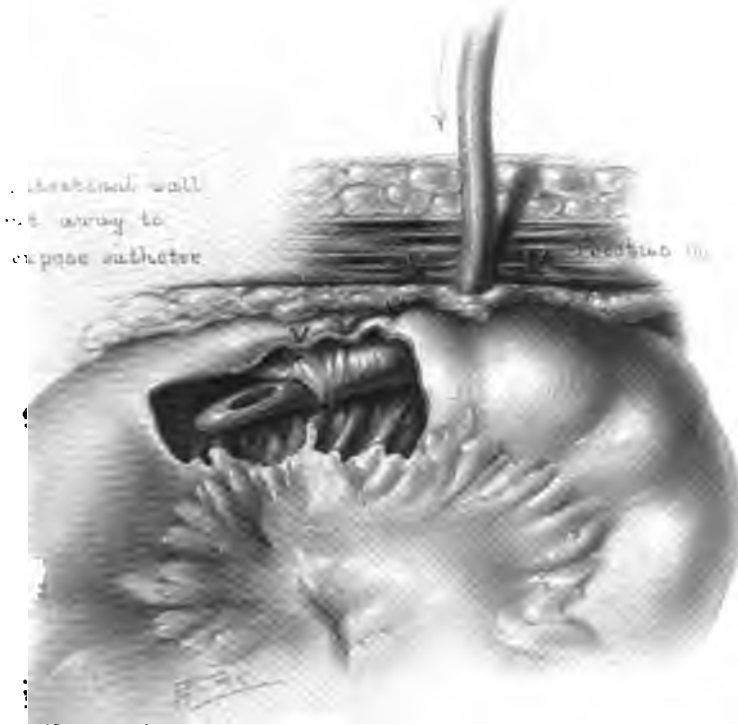
Fig. 35.—Tube enfolded in wall of bowel, passing through omentum and abdominal wall.

catheter passed through it. The use of the omentum in this way aids in preventing leakage after the removal of the catheter, and adds to the mobility of the intestine after the operation. The catheter may be brought out through the incision, in which case sutures are passed through the peritoneum, the omentum, and the intestine on each side of the tube, to hold it in position. In some cases a small perforation is

made through the abdominal wall, a little to one side of the working incision, and sutures are adjusted beneath the opening. When the perforation is made for obstruction, it is usually sufficient to leave the catheter in place from seven to twelve days. When made for purposes of nutrition, it is permanent in case of cancer, and is left as long as necessary in cases of persistent vomiting, since the stomach may be tested at any time, employing the tube when necessary.

The operation of jejunostomy has been made in our Clinic in 43 cases for nutritive purposes since 1910. In the larger number of the cases the operation was necessitated by cancer, and it was palliative. Because of the serious condition of the patients, the primary mortality was high and the palliation brief. The operation is not one of great utility, except in a few rare cases of non-malignant obstruction or for the temporary relief of gastric fistula following perforation and operation. Twelve of the 43 patients died within a week, 4 died within a month, 4 within two months, 7 within a year, and 3 within a year and a half. Thus in all of these cases the operation served its purpose, namely, that of affording temporary or permanent relief of the condition which necessitated the operation.

Summarizing: Jejunostomy for nutrition is of occasional value; jejunostomy or other enterostomy for intestinal obstruction is of great value.

CHRONIC ULCERATIVE COLITIS AND ITS ROENT-GENOLOGIC FINDINGS*

F. B. McMAHON AND R. D. CARMAN

This paper comprises a study of a group of cases of chronic ulcerative colitis in which marked pathologic changes occur in the intestinal wall, resulting in inflammatory thickening, contraction, granulation, or ulceration.

Chronic ulcerative colitis is a disease that is constantly attracting more attention from both the medical and the surgical members of the profession. The number of patients affected with the disease is increasing, probably because the number of cures do not keep pace with the annual incidence of the disease. We have recently reviewed the cases of chronic colitis of this type in the Mayo Clinic in which a roentgen examination of the colon was made, and we wish to submit a résumé of the subject, including certain roentgen findings that we believe are of particular importance and have not been sufficiently emphasized (Fig. 36).

The etiology in these cases of colitis is obscure. It is probably due to some constitutional derangement with a low grade of intoxication that seems to affect primarily the mucous lining of the large intestine, and at times the terminal portion of the ileum. Chronic constipation probably plays a part as a predisposing factor but does not explain all. It may be due primarily to some specific organism upon which is superimposed considerable localized trauma, local irritation, and mixed infections. The rectum and sigmoid are first and always the most severely affected, but eventually the process tends to become diffuse throughout the entire colon and occasionally the lower 12 to 24 inches of the terminal ileum. The early changes occur in the mucosa, which becomes reddened, thickened, and infiltrated with serum and blood-cells. This chronic inflammatory reaction results in the formation of granulation tissue. The mucous glands are increased in number and hypertrophied,

or they may become atrophic, small, or cystic. The mucous folds are increased or decreased in number and lose their normal appearance. There is an overproduction and hypersecretion of mucus. Polyps and

Fig. 36.—(106451.) Normal colon.

pedunculated papillomas may be formed. Localized superficial erosions and chronic ulcerations are frequently superimposed on all these changes, especially when there are polyps and papillomas, giving rise to deeper mixed infection and more profuse bleeding. In the severe and long-standing cases localized abscesses and extensive tissue destruction of the mucosa and the submucosa complicate the disease. The remaining structures of the bowel-wall undergo corresponding inflammatory changes and they may occur quite early. There is always an edema and lymphocytic infiltration and exudation in the other coats of the intestinal wall accompanying the changes in the mucosa. The coats are congested and thickened, multiple minute areas of scar tissue are formed, the bowel is contracted down, and is comparatively less yielding and less flexible (Fig. 37). Invariably the serosa is covered with a fibrinoplastic lymph exudate and becomes devoid of its normal luster. Frequently the peritoneal cavity contains a small amount of fluid and lymph.

The symptomatology is quite well known. There is usually a history of seasonal spells of chronic diarrhea and spurious diarrhea, with five to twenty, or more, stools per day over a period of weeks or months at a time for many years. The stools usually are thin and watery and contain much mucus, blood, and pus in varying amounts, depending on the duration and the severity of the disease. There may be traces of partially undigested food particles in the stools. There are intervals of complete or partial relief, during which time constipation may be present or the symptoms may be mild and more or less continuous, with a history of acute exacerbations from time to time. The use of the coarser and irritating foods usually exaggerates the condition, and dietetic indiscretions often precipitate an attack. Pain and tenderness are often absent. When present, they vary from a diffuse or localized abdominal soreness on pressure to severe tenderness and marked muscular rigidity. The left lower quadrant of the abdomen is the area most commonly affected, but this condition may be present over the course of the entire colon. Rectal tenesmus and pain at defecation are often distressing symptoms.

Loss of weight is common during severe attacks, but patients usually regain in the intervals. In some cases the patient is surprisingly well nourished and well developed. Nausea and vomiting are unusual and the appetite is ordinarily very good. An acute attack may prove fatal in a few weeks or months from prostration, desiccation, repeated

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intestinal hemorrhages, or from perforation of the bowel with general peritonitis.

Fig. 37.—(126013.) Female, age twenty-five years. Chronic colitis of eight years' duration. Roentgenogram shows a small smooth colon, with absence of haustra especially well marked from the hepatic flexure onward. Ileocecal valve incompetent.

In the event of other pronounced constitutional symptoms, or of the stools containing much blood, there is a moderate or severe grade of

secondary anemia. There may be a slight leukocytosis, and in the presence of tissue destruction and mixed infection there is always present an increase in the white blood count with a moderate predominance of polynuclear cells. Eosinophilia is rare. Digital examination of the rectum usually reveals a roughened and granular mucosa which is hypersensitive, painful, and bleeds easily. The anal sphincter is usually very spastic. The disease is resistant to almost all forms of medical treatment, although palliative measures may control the symptoms to a large extent for long periods of time. Spontaneous remissions are common in the milder stages and forms of the disease.

The incidence of the disease is slightly larger in males than in females, but there is very little difference, and the disease runs about the same clinical course in both sexes. Rural people and those living in the smaller towns appear to be more commonly affected. There seems to be no particular geographic distribution of the cases examined in the Mayo Clinic.

Repeated stool examinations are always essential, as it is necessary to rule out the more common causes of chronic diarrhea. In these cases no intestinal parasites are found. It must be remembered, however, that in an endamebic colitis that has been treated with emetin, the stools may be free from parasites on several examinations and still some of the symptoms persist. Theoretically, tuberculous and other specific bacterial infections can be identified by centrifugalization of a small portion of the stool content and microscopic examination of properly stained smears. There is also usually a suggestive history and other symptoms and physical signs present in tuberculous and bacillary colitis cases. A history of luetic infection, other constitutional stigmas, and the Wassermann reaction will put one on guard for the possibility of a syphilitic lesion in the lower part of the intestinal tract, although, of course, both conditions may be present. Fortunately syphilis of the rectum and colon is very rare.

The proctoscopic examination is an efficient aid in the differential diagnosis, and in ruling out a low-lying malignancy, either alone or superimposed on some other chronic process. Proctoscopic examination usually reveals a chronic indurative proctitis and sigmoiditis of a granular type which bleeds easily with a few ulcerations irregularly distributed. Occasionally small polyps or papillomas may be seen. Frequently it is only by removing a small piece of suspicious tissue and subjecting it to

careful microscopic examination that malignancy and the infectious granulomas of the rectum can reasonably be excluded.

Very little has been written concerning the signs elicited in the roentgen examination of chronic ulcerative colitis, and no great importance has been attached to roentgenologic findings in the disease up to this time. In 1912 Schwarz,[1] of Vienna, described the characteristic features in a small number of cases of chronic ulcerative colitis. Among other things he included the phenomena of a small and smooth bowel, absence of haustration, and incompetence of the ileocecal valve (Fig. 38). We have found from an examination of a number of colons in chronic colitis that these conditions are invariably present and we believe that their importance should be emphasized. These roentgenologic phenomena are not due to spasm, but result from the organic alterations in the bowel-wall, because definite pathologic changes are found in both the gross and the microscopic appearance of all the coats. Furthermore, they are permanent and cannot be altered in their main appearances and characteristics by the administration of antispasmodics to physiologic effect prior to a second roentgen examination. Besides, enterospasm has not been observed by us during the roentgen examination in this type of colitis.

There are certain other conditions of the large bowel in which some of these phenomena may also be found to a varying degree; but, as a rule, they can be eliminated either by a correlation of the roentgen findings with the clinical data, or the roentgen picture alone may definitely indicate a lesion other than colitis. For example, in an occasional case of chronic constipation, the large bowel may be smooth and show no haustration (Fig. 39). Exceptionally also, in cancer of the colon, the unaffected portion of the bowel may have smooth, unhaustrated borders (Fig. 40). However, these findings are not constant. In such instances the lack of haustration is doubtless due to relaxation of the longitudinal muscle bands—the tænia.

The incompetence of the ileocecal valve, which has been noted rather constantly in cases of chronic ulcerative colitis, is not of itself diagnostically important, since we find it in a very high percentage of all cases examined, whether normal or pathologic. But, in conjunction with other roentgen signs of chronic ulcerative colitis, it may have some corroborative value, when the barium runs into the ileum spontaneously and profusely.

It is worthy of note that in a limited number of cases of chronic endamebic colitis examined, we did not find a roentgenologic picture in

any measure differing from the normal. The group included cases of long standing and of recent exacerbations, but none that were prostrated.

Fig. 38.—(107128.) Male, age fifty-four. Clinical diagnosis of chronic colitis of eleven years' duration. Roentgenogram shows a narrow, smooth, sausage-like colon. Both flexures ptosed. Incompetent ileocecal valve. No haustration seen.

Sanford[2] has emphasized the fact that the entire syndrome of chronic endamebic colitis as seen in the North is not so severe as in the South

and the tropics, which may explain the absence of marked pathologic changes in the bowel-wall. However that may be, we believe that the

Fig. 39.—(12716.) Female, age fifty-seven years. History of chronic constipation and migraine for a period of twenty-five years. Roentgenogram shows marked redundancy of the colon. Incompetent ileocecal valve. The bowel is smooth and its outline is practically without haustration, but the colon is not contracted. Further, the history distinguishes the case from a chronic ulcerative colitis.

roentgen examination offers distinct value in the differentiation of these two diseases, especially as seen in this latitude.

Our own experience suggests that the roentgen findings when carefully correlated with the clinical history can be made of much use in the diagnosis of chronic ulcerative colitis. The roentgenogram also enables

Fig. 40.—(144665.) Female, age forty-four years. Filling defect in the right half of the transverse colon. Roentgen diagnosis: Carcinoma. The remaining bowel is smooth and unhaustrated, but not contracted. The filling defect was produced by a carcinoma, as proved at operation.

a more accurate estimate of the extent of involvement and thus may serve as a guide in determining whether the treatment shall be medical or surgical.

Fig. 41.—(146817.)

Both roentgenoscopy and roentgenography were employed in the cases herewith reported. The enema was preferred to the ingested meal.

In an extensive case of long standing the capacity of the colon is materially lessened. It fills very rapidly, and if the clyster is administered with much force, the patient is very likely to expel it before the roentgen observations are completed.

The following illustrative cases were selected from the group studied:

CASE 146817.—Male, aged thirty-eight; shoemaker. Registered November 30, 1915.

Previous History.—Pneumonia April, 1915.

Present Illness.—For two years spells of diarrhea with 15 to 20 stools per day of a thin, watery character, with much mucus and at times blood stained; odor not offensive. With attacks there was loss of weight and strength. During the past four months, interval of but two weeks when he was free from severe symptoms, and during the past three months there has been considerable bright red blood in the stools, much abdominal, cramp-like colic, and rectal tenesmus. Never any chills or fever noted.

Physical Examination.—Considerable emaciation. Evidence of moderate anemia. Pyorrhea alveolaris and gingivitis present. Palpable liver margin. Slight tympanitis and slight diffuse abdominal tenderness. Digital examination of rectum negative.

Urinalysis.—Negative.

Blood Examination.—Hemoglobin 70 per cent; 4,520,000 red blood-cells; 10,000 white blood-cells; 38 per cent polymorphonuclear leukocytes; 44.3 per cent small lymphocytes; 16.7 per cent large lymphocytes; 1 per cent eosinophiles. Wassermann, negative.

Stool Examination.—Red blood-cells and pus-cells present, no parasites found. Culture from stool negative for Shiga bacilli.

Roentgen Examination.—Colon, small and smooth throughout. No visible haustration. Ileocecal valve incompetent (Fig. 41).

Clinical Diagnosis.—Chronic ulcerative colitis; pyorrhea alveolaris and gingivitis.

Operative Findings.—Colon contracted to about caliber of small intestine, and presents appearance of a chronic inflammatory reaction with thickened and edematous walls, increasing in severity from cecum downward to rectum.

Operation.—Ileostomy (Brown)—appendectomy secondary.

CASE 134997.—Female, aged thirty-three. Housewife. Registered September 13, 1915.

Previous History.—Negative.

Present Illness.—A nine-year history of chronic constipation with passage of some mucus in the stools, and at times blood tinged. For the past two years constipation has been more marked, requiring brisk laxatives or purgatives, which in turn caused a diarrhea that required medicine to control. For the past six months she has complained of

diarrhea and spurious diarrhea associated with the passing of mucus streaked with bright red blood, also cramp-like abdominal pains and rectal tenesmus. Normal weight, 107 pounds; present weight, 97 pounds.

Fig. 42.—(134997.)

Physical Examination.—Thin and pale in appearance. Marked intestinal peristalsis demonstrable. Digital examination of the rectum painful; rectal mucosa roughened and congested.

Urinalysis.—Negative.

Blood Examination.—Hemoglobin 60 per cent; 4,500,000 red blood-cells; 14,400 white blood-cells, and a normal differential count. The Wassermann was negative.

Stool Examination.—Red blood-cells and pus-cells present, no parasites found.

Proctoscopic Examination.—Chronic proctitis and sigmoiditis with some superficial ulcerations.

Roentgen Examination.—The left arm of the transverse colon, the splenic flexure, the descending colon, and the sigmoid are small, smooth, and unhaustrated. This condition was unchanged after the administration of an antispasmodic to physiologic effect. Note that the disease is limited to the left half of the large bowel, as shown in the roentgenogram (Fig. 42).

Clinical Diagnosis.—Chronic ulcerative colitis.

Operative Findings.—Chronic ulcerative colitis.

Operation.—Ileostomy (Brown)—appendectomy secondary.

CASE 160059.—Female, aged twenty-eight. Clerk. Registered May 18, 1916.

Previous History.—Negative except appendectomy ten years previously elsewhere.

Present Illness.—For twelve years she had had spells of diarrhea and bloody stools associated with loss of weight and strength. Some temporary relief with medical, dietetic, and local treatment. She has been without symptoms as long as a year at a time. At the present time there are from six to eight stools daily, containing much blood and mucus and associated with considerable tenesmus.

Physical Examination.—Negative except for some tenderness over the entire colon and considerable tenderness on digital examination of rectum.

Urinalysis.—Negative.

Blood Examination.—Hemoglobin 80 per cent.

Stool Examination.—Negative for parasites.

Proctoscopic Examination.—Examination very difficult on account of the contracted condition of the rectum. Marked proctitis which bleeds easily. No gross ulcerations. The sigmoid could not be examined on account of spasm.

Roentgen Examination.—Beginning at the hepatic flexure, the colon was smooth, contracted, and without haustral markings. The narrowing was most marked in the left half of the transverse colon, the descending colon, and the sigmoid. The transverse colon was redundant. Ileocecal valve incompetent (Fig. 43).

Clinical Diagnosis.—Chronic granular colitis.

Operative Findings.—Granular type of chronic colitis. Definite

thickening and narrowing of the colon wall. Slight injection of its blood-vessels. Appendix removed at former operation elsewhere.

Operation.—Ileostomy (Brown).

Necropsy.—General peritonitis. Colon showed chronic inflammatory changes with marked thickening throughout its entire wall and many
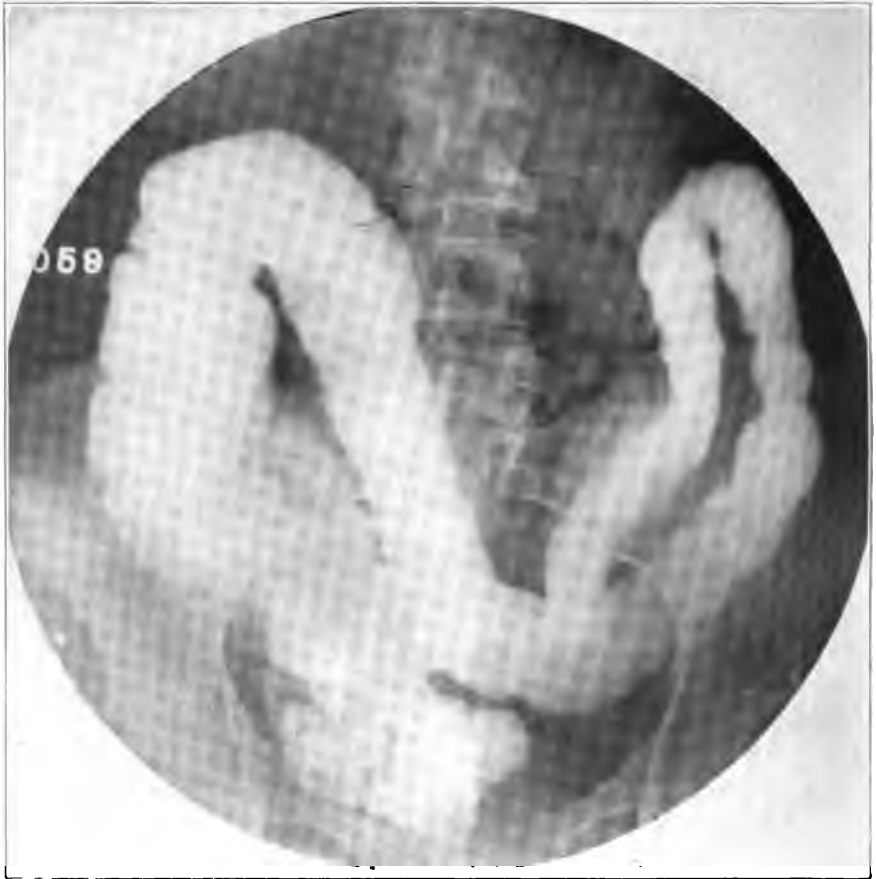

Fig. 43.—(160059.)

petechial hemorrhages, old and recent, in its mucosa. No ulcerations. Small papilloma in the descending colon.

CASE 172507.—Male, aged thirty-five. Iowa farmer. Registered September 14, 1916.

Previous History.—Negative.

Present Illness.—For three years there have been spells of diarrhea

with blood-stained mucus in the stools, and associated with rectal tenesmus. The early spells were of about six weeks' duration. Con-

Fig. 44.—(172507.)

siderable loss of weight with each attack. During the past fourteen months the symptoms have been practically continuous and the stools contained considerable blood. For the bleeding he had had a cauteriza-

tion of the rectal mucosa elsewhere with practically no improvement. For the three weeks prior to admission to the Clinic he had had 10 to 20 stools per day, containing much blood and mucus. History of slight fever at times during past month.

Physical Examination.—Twenty pounds loss of weight. Evidence of anemia. Slightly tender over entire abdomen. Digital examination of rectum painful and difficult.

Urinalysis.—Negative.

Blood Examination.—Marked secondary anemia with an average hemoglobin of 34 per cent. Wassermann negative.

Stool Examination.—Negative for parasites; red blood-cells and pus-cells present.

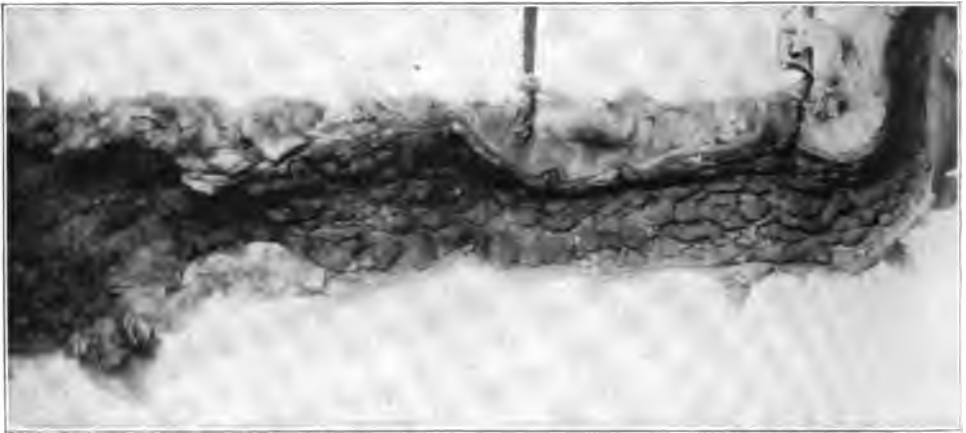*Proctoscopic Examination.*—External and internal hemorrhoids were

Fig. 45.—(172507.)

found, but not sufficient to account for all symptoms. Large fissure into rectum. Indurated area in anterior wall of rectum two inches up.

Roentgen Examination.—Roentgenoscopy: Entire colon smooth, contracted, and without haustration. Roentgenogram (after involuntary partial evacuation): Hepatic flexure, descending colon, and sigmoid mottled in appearance; ileocecal valve incompetent (Fig. 44).

Clinical Diagnosis.—Fissure of rectum (postoperative), hemorrhoids; chronic ulcerative colitis; secondary anemia.

Clinical Notations.—Medical and dietetic treatment and blood transfusion without improvement. Died thirteen days after admission.

Necropsy.—Chronic inflammatory changes in the wall of the large bowel with marked diffuse edema and thickening of all its coats. The mucosa shows chronic ulcerations in the lower colon and rectum (Fig. 45).

Conclusions

1. There is a group or chain of subjective and objective symptoms that is quite characteristic of chronic ulcerative colitis.

2. There are definite organic changes in all the coats of the colon wall in chronic ulcerative colitis, resulting from chronic inflammatory reaction with edema, lymphocytic infiltration, thickening, scar tissue formation, and contraction.

3. The roentgen examination in these cases shows the colon to be small, smooth, and without haustration in the part or parts affected.

4. A more accurate estimate as to the extent and severity of the involvement can be obtained by a correlation of the clinical history with the roentgen findings.

5. The roentgenogram will frequently be an aid in determining the course of subsequent treatment.

6. In a limited number of examinations we have not found cases of chronic endamebic colitis which furnish any characteristic or similar roentgen findings. Therefore, it appears to be an aid in differentiating amebic from chronic ulcerative colitis.

REFERENCES

1. Schwarz, G.: Klinische Roentgendiagnostik des Dickdarms. Springer, Berlin, 1914, 153 pp.
2. Sanford, Arthur H.: The geographic distribution of amebiasis, Jour. Am. Med. Assn., 1916, lxvii, 1923–1926.

THE SIGNIFICANCE OF LAMBLIA INTESTINALIS IN THE STOOL*

A. H. LOGAN AND A. H. SANFORD

That certain protozoal parasites have a definite pathogenicity in some forms of intestinal disturbances is acknowledged by practically all clinicians. The rôle played by the flagellate, Lamblia intestinalis, is still an open question if one is to judge by the diversity of opinion expressed in the literature on the subject. In the writings of Braun, Park and Williams, Barker, Besson, Allbutt and Rolleston, and many others, it is tersely stated that they are non-pathogenic. Other writers, among them Emerson, Stiles, Rodenwaldt, MacNeal, and Neveu-Lemaire, consider that their part as an etiologic factor in chronic diarrhea is not entirely settled, but that they may have much to do in prolonging symptoms when the disease is once established. On the other hand, Daniels, Brumpt, and Stitt each ascribe a pathogenic rôle to these organisms, the last-mentioned author stating that they are "responsible for a chronic and intractable diarrhea, an infection only minor in importance to amebic infection."

We have not attempted to review the literature fully, but may state that in recent articles on the subject Lamblia intestinalis has been considered pathogenic by the following authors: Du Bois and Toro, Wenyon, Russell, Kennedy and Rosewarne, Porter, Fantham, Fantham and Porter, and Mathis.

In tropical regions this parasite is encountered very frequently in stool examinations. In our country, especially in northern latitudes, it is not found commonly. The cysts are easily recognized, and when present are found in great numbers if the patient has had the usual preparation for examination for endamebas, i. e., one-half to one ounce of salts before breakfast. It is quite usual, when cysts are present, to

* Reprinted from the Journal of Lab. and Clin. Med., 1917, ii, 618–621.

find free, motile forms the next morning after the patient has taken a second dose of salts.

In stool examinations made for more than 6000 patients during the past six years we have found this parasite in only a trifle more than 1 per cent of the cases. The patients came from all parts of the United States, but chiefly from the northern states; three were from Canada.

This report, then, is based on 66 cases in which Lamblia intestinalis has been found in stool examinations. In 41 persons this was the only organism that might account for the complaint. In the remaining 25 cases there were other organisms, or pathologic conditions which presumably, in some instances at least, accounted for the complaint.

In studying the histories of these cases we find there is apparently no syndrome which is diagnostic without a stool examination. A history of preceding or present diarrhea, usually without blood or mucus, often with most or all of the stools in the early morning hours, with rumbling and rolling in the intestines, indefinite pain slightly more to the right side, an "all-in" feeling, and nervous indigestion are all suggestive symptoms, but in no way diagnostic. After the initial attack of diarrhea, constant looseness, alternate constipation and diarrhea, or constipation may remain.

As lamblias have been held to be non-pathogenic by most observers, no attention has been paid to their presence in the stools, and little or no treatment has been directed toward their removal. Possibly for this reason many of our patients give long histories. Nineteen of the series of 41 patients gave a history extending over five years, 11 of them having a constant looseness or severe diarrhea. Eighteen of the series had constant looseness varying from 3 to 20 stools daily; 8 others had spells of diarrhea; 3 had normal stools; and the remainder were constipated.

As the lamblias inhabit the upper intestinal tract, we would not expect free blood in the stools or much inflammation in the colon. Six of the 41 patients had seen some free blood (one of these had bleeding piles), 18 expressly stated that no blood had been passed, and in the other cases no mention of blood was recorded. In the 25 cases in which there were complications, 5 patients had noted blood and 13 had not.

Proctoscopic examinations were made for 10 of the 41 patients. Six had normal bowels, 3 a slight proctitis, and 1 a diffuse colitis without ulceration. Of 5 patients in the series of 25 who had proctoscopic

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examinations, 2 had normal bowels, 1 a mild colitis, and 2 ulceration due to amebas.

Twelve of the series with lamblias alone had examinations of the stomach. In 9 the acids were normal, and in 3 there was absence of hydrochloric acid. Six patients had barium roentgenographic examinations of the stomach, and in all the findings were negative. Blood examinations were made in the majority of the cases, but showed no change in the eosinophiles, and in only two patients of the larger series was the hemoglobin reduced (45 per cent).

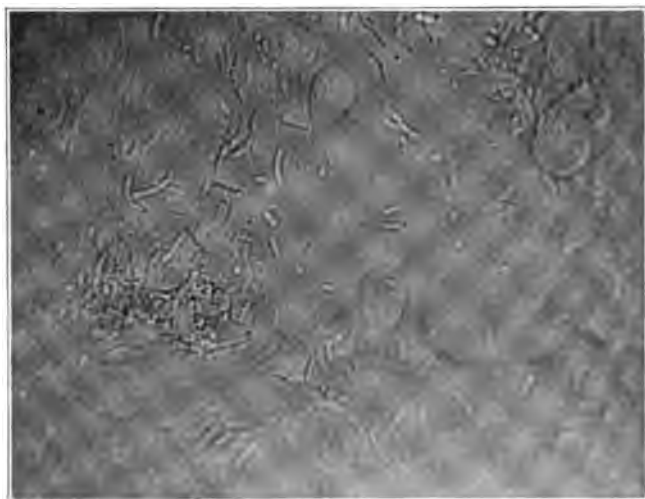Since the symptoms definitely indicated some trouble and in many

Fig. 46.—Photomicrograph of Lamblia intestinalis.

cases were of long duration, and since lamblias were not considered pathogenic, other organs than the intestines were suspected to be the site of the trouble. Ten of the 41 patients were operated on, and 3 of the other group of 25. One of the 10 had carcinoma of the rectum and was operated on five years after we first found the lamblias. One was operated on for enlarged spleen which later turned out to be a lymphosarcoma. Five had appendicectomies; 4 were not helped; the fifth had had a history of several definite attacks of appendicitis, and was relieved of that trouble. On 2 cholecystectomies were done without relief; and in 1 the gallbladder was the surgical objective, but was found

normal. In this case a pericolitis was considered the cause of the trouble. Three other patients had surgical diagnoses—1 a diagnosis of appendicitis, 1 of cholecystitis, and 1 of duodenal ulcer—but were not operated on.

Of the 3 operations in the second group, 1 appendicectomy gave no relief, 1 cholecystectomy and appendicectomy gave no relief, and 1 appendicectomy on a patient with a history of 10 definite attacks of appendicitis gave relief.

Nine only of the 41 patients were treated in the Clinic, and these for a short time only. Thymol and methylene-blue were used. Thymol, given in 6 instances, relieved the symptoms temporarily, and removed lamblias from the stools in 4 cases. However, only one stool test was made after treatment in each instance. In 1 case a severe diarrhea was stopped and the patient gained 27 pounds, but four months later the symptoms recurred. In another case the diarrhea stopped and the hemoglobin rose from 45 per cent to 68 per cent in one month. Methylene-blue was of benefit in only 1 case.

In 10 of the cases in which amebas were a complication, treatment consisted of emetin, ipecac, and coal-oil enemas, the lamblias being disregarded. Five of these were symptomatically relieved, though in 1 case there was a recurrence in six weeks. In none did this treatment remove the lamblias. In 1 instance in which both lamblias and amebas were present the patient was treated with thymol and coal-oil enemas; both organisms were removed, and the patient was relieved of the diarrhea.

Thus it is likely that when the pathogenicity of these parasites has been disregarded, the diagnosis and treatment of many patients have not been correct; and that when Lamblia intestinalis has been considered the cause of the condition, and treatment has been instituted against it, better results have been obtained.

CONCLUSIONS

1. Lamblia intestinalis should probably be considered a pathogenic parasite.

2. We have obtained no definite syndrome in our series.

3. The removal of lamblias is difficult.

4. The best results have been obtained from thymol medication.

TWENTY-FIVE CASES OF LAMBLIA INTESTINALIS WITH OTHER COMPLICATIONS

COMPLICATIONS	CASES
Endameba histolytica	9
Endameba histolytica and active pulmonary tuberculosis	1
Endameba histolytica and history of passing recent tapeworm and hookworm	1
Actively motile ameba (not diagnosed)	1
Non-motile ameba	2
Encysted Endameba coli	2
Endameba coli	2
Ova of tenia	1
Active pulmonary tuberculosis	4
(1 with tuberculous peritonitis)	
(1 tubercle bacilli found in stools)	
(1 pulmonary symptoms came eighteen months after abdominal symptoms)	
Pernicious anemia	2

REFERENCES

Allbutt, F. C., and Rolleston, H. D.: System of medicine, Macmillan Co., London, 1906–11, ii, Part 2, 55.

Barker, L. F.: Monographic medicine, D. Appleton & Co., New York, 1916, iii.

Besson, A.: Practical bacteriology, microbiology, and serum therapy, Longmans, London, 1913, 827.

Braun, M.: The animal parasites of man, Wm. Wood & Co., New York, 1906, 48.

Brumpt, E.: Précis de parasitologie, Masson, Paris, 1913, 198.

Daniels, C. W., and Newham, H. B.: Laboratory studies in tropical medicine, P. Blakiston's Son & Co., Phila., third ed., 1911, 368.

Du Bois, E. F., and Toro, W. C.: Two cases of infection with lamblia intestinalis, Proc. New York Path. Soc., 1912–13, n.s., xii, 32–37.

Emerson, C. P.: Clinical diagnosis, J. B. Lippincott Co., Phila., 2nd ed., 1908, 405–406.

Fantham, H. B.: Remarks on the nature and distribution of the parasites observed in the stools of 1305 dysenteric patients, Lancet, 1916, i, 1165.

Fantham, H. B., and Porter, A.: The pathogenicity of Giardia (Lamblia) intestinalis to man and to experimental animals, Brit. Med. Jour., 1916, ii, 139–141.

Kennedy, A. M., and Rosewarne, D. D.: Lamblia intestinalis infections from Gallipoli, Lancet, 1916, i, 1163–1165.

MacNeal, W. J.: Pathogenic microorganisms, P. Blakiston's Son & Co., Phila., 1914, 400.

Mathis, C.: Troubles intestinaux dus au protozoaire flagellé: Lamblia intestinalis, Bull. Soc. méd.-chir. de l'Indo-Chine, 1914, v, 55–62.

Nevu-Lemaire, M.: Précis de parasitologie humaine, Rudeval, Paris, 1908, 267.

Park, W. H., and Williams, A. W.: Pathogenic microorganisms, Lea & Febiger, Philadelphia, fourth ed., 1910, 586.

Porter, A.: An enumerative study of the cysts of Giardia (Lamblia) intestinalis in human dysenteric fæces, Lancet, 1916, i, 1166–1169.

Rodenwaldt, E.: Flagellaten (Trichomonas, Lamblia), In v. Prowazek, S.: Handbuch der pathogenen Protozoen, Barth, Leipzig, 1912, i, 88–95.

Russell, B. R. G.: Intestinal disorders arising from protozoal infection, Lancet, 1916, i, 1161–1163.

Stiles, C W.: The internal parasites of rats and mice in their relation to diseases of man, In: The rat and its relation to the public health, Govt. Printing Office, 1910, p. 87.

Stitt, E. R.: Practical bacteriology, blood work, and animal parasitology, P. Blakiston's Son & Co., Phila., 1910, 202.

Wenyon, C. M.: The common intestinal protozoa of man, Lancet, 1915, ii, 1173–1183.

DIVERTICULITIS OF THE LARGE INTESTINE*

W. J. MAYO

In a paper on acquired diverticulitis of the large intestine, in 1907, Wilson, Giffin, and I[1] were able to demonstrate the pathology and to outline the clinical history of the condition to which Graser[2] called attention in 1898. Our five cases in which the diverticulous sigmoid was excised proved to be the first recorded in which an actual demonstration of the pathology of diverticulitis was established during life. Articles dealing with postmortem demonstrations of diverticula of the colon had been rather frequent,[3] and suggested an explanation of clinical experiences such as those recorded in the contributions of Telling,[4] Brewer,[5] Beer,[6] Plummer,[7] and others.

Since the recognition of the condition we have resected portions of the large intestine for diverticulosis in 42 cases. In 36 the sigmoid was involved, in 1 the transverse colon, in 1 the ascending colon, in 1 the hepatic flexure and cecum, in 1 the rectosigmoid juncture, and in 2 the rectum. The number of cases in which resection was not done but in which the patient was operated on for abscess, fistula, etc., is not given, because the presence of diverticula was not proved by the demonstration of the specimen. The diverticula were all of the acquired variety; that is, the mucous coat pouched through small openings in the musculature in contradistinction to true diverticula of the congenital, traction, or pulsion types in which all the intestinal coats cover the sac. The diverticula were multiple and occurred at any weak point in the circumference of the colonic wall, such as vessel holes or muscle defects. From 1 to 8 inches of the intestine were seriously involved, although much longer stretches showed a diverticulous tendency. Hardened masses of feces were often found in the distal extremity of the narrow-necked diverticula, although, as a rule, only one or two of the diverticula were directly responsible for the existing diverticulitis and peridiverticulitis.

The signs and symptoms closely resembled those of appendical inflammation, with the marked difference that in the great majority of instances the disorder was on the left side of the abdomen. It is altogether probable that most of the reported cases of so-called "sigmoiditis" are examples of diverticulitis.

Of the 42 patients in whom resection was done, 66.6 per cent were males and 33.4 per cent females. The average age was fifty-three years. The youngest patient was twenty-seven years of age and the oldest seventy-three. The average weight was 175½ pounds. The heaviest patient weighed 225 pounds, the lightest, 120 pounds. Those of light weight were below their average weight for the previous ten-year period. In many cases increased deposit of fat in the abdominal cavity undoubtedly had some influence in the development of the diverticula, especially if there had been a tendency to the formation of intestinal gases. The average duration of symptoms was two years; the longest twelve years; the shortest seven days.

In 34 of the 42 patients a sensitive tumor was present in the left iliac fossa during the attack, which was attended by localized peritonitis and often by intestinal obstruction. In two patients diverticula were found in the rectum. C. H. Mayo[8] has shown that occasionally a deep-seated infection about the rectum eventuating in long fistulous tracts extending from the perianal region into the pelvis has this origin. Twenty patients had pain in the left iliac fossa. In 32 constipation was marked. A diagnosis of inflammatory disease was made in 20 of the 42 cases. The roentgen ray showed obstruction, but in acute obstructions it did not differentiate diverticulitis from carcinoma, although it usually made the differentiation in chronic disease. Carcinoma was present in 13 cases (31 per cent).

Clinically, cases of diverticulitis may be readily classified into four groups:

GROUP 1.—*Self-limiting diverticulitis and peridiverticulitis.*—This group includes fleshy, middle-aged persons who present themselves with an acute sensitive tumefaction in the left iliac fossa. The mass gradually disappears in the course of some days, with restoration to health. The disturbance is due to irritation of fecal concretions, dead epithelium, and other contents in the thin-walled, narrow-necked sacs, which cause obstruction from edema and infection and penetration of bacteria to the peritoneal surface. There is marked tendency to relapse quite similar in character to that of relapsing appendicitis, and in the early

histories of the patients of Groups 2, 3, and 4, it will often be found that several such attacks had occurred before the severe attack which necessitated surgical interference. That diverticulitis does not always produce trouble is shown by the relative frequency with which this condition is found postmortem, by the frequency with which diverticula of the sigmoid are a chance finding in the course of abdominal operations for other purposes, and by the frequency with which routine roentgen-ray examination of the colon shows symptomless diverticula. We should not assume, therefore, that the presence of these diverticula, or even a single mild attack of diverticulitis which quickly subsides without obstruction or other serious symptoms, necessitates operation. Patients of this kind are often poor surgical risks from other causes, such as obesity, and a considerable mortality attends resection, the only operation that really cures the disease. It is only in those cases, therefore, in which the symptoms are serious or the disease becomes chronic or relapsing that operation is to be considered.

GROUP 2.—*Diverticulitis and peridiverticulitis with formation of abscess resulting in enterovesical, enterocutaneous, and other fistulas.*—This group includes those cases in which infections—either a developing peritonitis with abscess formation or the results of infectious processes which connect the diseased colon with the cutaneous surface, the bladder, or neighboring intestine—lead to the necessity for surgical interference. The rule is that if an abscess forms it should be opened and drained, but a serious attempt should not be made at the primary operation to remove either the infected diverticula or the section of colon which contains them. None of our patients has died from a general septic peritonitis as the primary result of diverticulitis, although such cases have been reported. The management of cases of complicated fistulas in which there are openings into the bladder and colon and to the cutaneous surface, and especially that most common type in which an internal fistula connects the bladder and the sigmoid, is very difficult. The obesity of the patient and the enormous amount of scar tissue which surrounds the fistulous tracts add greatly to the operative difficulties. In enterovesical fistulas we have opened the peritoneal cavity, dissected out the fistulous tracts, and closed the openings in the bladder and colon with chromic catgut sutures. Rarely was the result immediately satisfactory. As a rule, a temporary fecal fistula to the surface formed after a few days, but when, following operation, the bladder and sigmoid were kept separated by rolls of rubber tissue, and especially when the

sutured opening in the sigmoid was protected by omentum, these secondary fistulas eventually closed spontaneously. A retention catheter has been placed in the bladder for a week and a rubber tube fastened into the rectum following operation, to relieve tension.

GROUP 3.—*Obstruction.*—In acute diverticulitis the obstruction is the result of infection and edema. Chronic obstruction is due to hyperplasia, adhesions, and angulation—the hyperplastic stenosing type. The

Fig. 47.—Symptomless diverticula of the sigmoid.

condition is practically identical with those in Groups 1 and 2, but the addition of the obstruction in these cases is so serious a feature that it seems best to classify them independently. It was most surprising, however, when the entire mass was dissected out and the diseased bowel laid open, to find so little actual obstruction. In this group a tumor is usually found, and in 31 per cent malignant disease coexists. I do not know of a more difficult differentiation than to foretell whether a given obstructing tumor deep in the iliac fossa of an adipose patient is diver-

ticulitis or carcinoma or both.   On a number of occasions I have gone
down on such tumors which had been explored and pronounced inoper-
able by surgeons of skill and experience and, on dissecting the tumor out,
found that it was diverticulitis without carcinoma and that the enlarge-
ment of the lymphatic glands, which had been one of the determining
factors in estimating inoperability at the previous exploration, was due
to sepsis.   As a rule, the obstruction from diverticulitis is not quite

Fig. 48.—Symptomless diverticula of the sigmoid.

complete.   In this respect it differs from that of carcinoma, in which
condition complete obstruction may be the first symptom of the disease.
Several times, with great difficulty, I have dissected out a considerable
portion of the sigmoid and found that the infection involved only one
or two diverticula.   Therefore the offending diverticula might have been
excised and the patient spared the risk of the more serious operation.
In 2 cases it was possible to excise infected diverticula successfully
and separate the obstructing adhesions.   On a few occasions a tumor

was explored because of our inability to differentiate diverticulitis from carcinomatous disease. After a diagnosis of diverticulitis was estab-

Fig. 49.—Carcinoma of the sigmoid developing on diverticulitis. Specimen to be sectioned through orifices of diverticula, at lines A and B (see Figs. 50 and 51).

lished, drainage was instituted for the relief of the local peritoneal infection, with recovery of the patient. Fortunately, the roentgen ray now furnishes the differentiation in a high percentage of cases. In
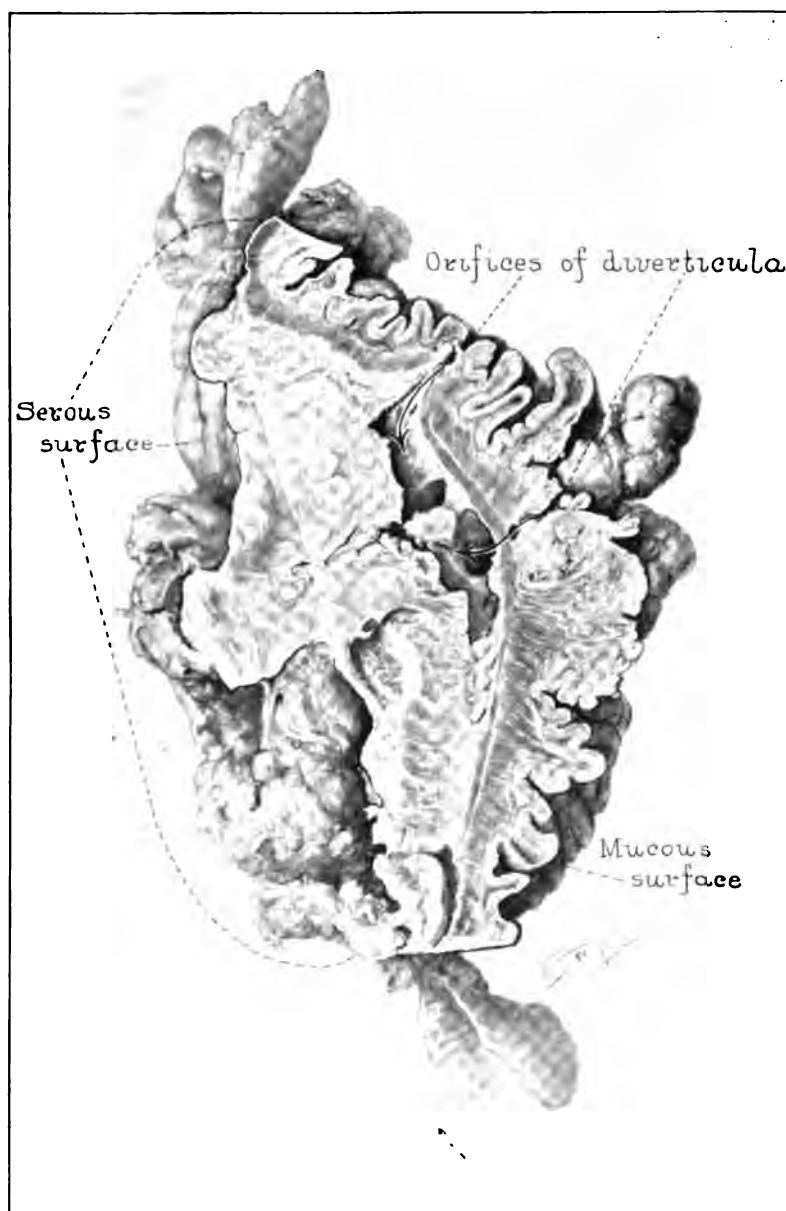
Fig. 50.—Half of the specimen shown in Fig. 49, after a longitudinal division at line *A*, showing courses of diverticula about which carcinoma has developed.

acute obstruction it may be necessary to make a colostomy close to the obstructing mass so that the colostomy and tumor may be excised together at a second operation; or perhaps a better plan is to do a complete ileostomy for temporary relief, then resect later, and finally, as a third stage, restore the ileum to the cecum.

GROUP 4.—*Carcinoma developing on a diverticulum.*—This group is of great interest. Among the 42 cases of resection for diverticulitis, there were 13 in which carcinoma coexisted. The carcinoma had such definite relationship to the diverticulitis as to make it reasonable to assume that infection and irritation by hardened fecal masses in diverticula were the cause of chronic irritation and precancerous change. The only known fact of importance in the etiology of carcinoma is its relation to chronic irritation. The term "precancer" is used to denote certain cell changes taking place in the area of chronic irritation which, if found in connection with invasion of the tissues, would be typical of carcinoma.

Giffin[9] found that for every sigmoid resected in our clinic for diverticulitis, seven had been resected for carcinoma. Our statistics show that in 300 resections for carcinoma, 180 were for sigmoid growths. In 42 cases of diverticulitis of the large intestine the diverticula were in the sigmoid in 36. It has often been pointed out that carcinoma of the colon, especially of the sigmoid, may progress very slowly. Cases have been reported in which a colostomy was made for the relief of obstruction due to supposed carcinoma; the patients lived for a number of years and then died with carcinoma of the sigmoid, a fact which apparently proved that the condition had been carcinoma from the beginning and that the natural course of the disease had continued for eight or nine years. This inference is unwarranted. We have operated in several cases of this type, and on resection of the growth found carcinoma developing on old diverticulitis. In tracing the early history it could be seen that the diverticulitis had been the cause of the obstruction for which the colostomy was done, and that the carcinoma had developed at a much later date as the result of the chronic irritation. In one rather remarkable case, a supposed carcinoma of the sigmoid, associated with a carcinoma of the transverse colon, was found on exploration. I removed the left half of the transverse colon, the splenic flexure, the descending colon, and part of the sigmoid, uniting the remainder of the transverse colon to the lower sigmoid. When the specimen was unraveled, it proved to be diverticulosis of six inches of the sigmoid. The

carcinoma had developed on one diverticulum which had become adherent to the transverse colon, and had spread into the peritoneal, muscular, and submucous coats of the transverse colon without penetrating the mucosa.   There was no carcinoma in the sigmoid, the malignant process being confined strictly to the diverticulum and the transverse colon. At the present time it is usually possible to differentiate between diverticulitis and carcinoma by the roentgen ray, since in carcinoma a filling defect will be found in addition to the less reliable findings of blood, pus, and mucus in the stool.   With the sigmoidoscope we have been able to
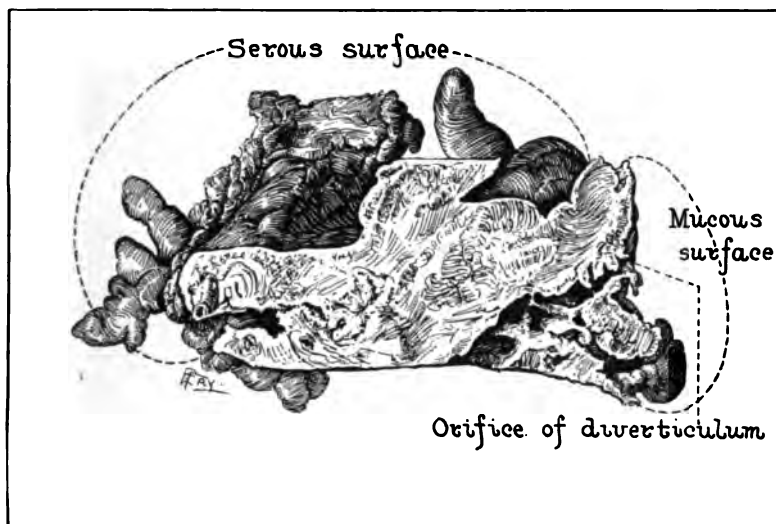
Fig. 51.—Half of section shown in Figs. 49 and 50 after a horizontal division at line *B*. Course of diverticulum through the orifice through which line *B* passes.

differentiate carcinoma associated with diverticulitis of the lower sigmoid and rectosigmoid, but have not been able to demonstrate diverticula.

Some of our patients with carcinoma associated with diverticula gave a long history of having had, at various times, inflammatory attacks with development of tumefactions which disappeared.   After the carcinoma developed, the symptoms became more or less continuous.   In reviewing a series of early specimens of sigmoid resected for supposed carcinoma, Wilson[10] found that three which had been resected years ago, before all specimens were subjected as a routine to microscopic examination, showed diverticulitis and no carcinoma.   The association of carcinoma with diverticulitis leads to the conclusion that when a tumor

appearing to be diverticulitis but without acute symptoms is found in the sigmoid or colon, and especially if the tumefaction only partially subsides and then continues as a chronic mass causing symptoms more or less marked, carcinomatous change is to be suspected and resection should be done. If there is definite obstruction at the time, or if the

Fig. 52.—Carcinoma developing on diverticulitis.

disease is advanced, the two-stage operation of Mikulicz, Bruns and Paul, as described by C. H. Mayo, may be adopted. Frequently, instead of leaving the tumor attached in the wound, we have cut the protruding bowel and tumor off, leaving the two ends of the intestine closed by a clamp on each, suturing the intestinal stumps into the wound

behind the clamps, and thoroughly covering the parts with petrolatum. After from twenty-four to forty-eight hours, or as long as the patient was able to stand the gas pressure from the complete obstruction, the clamps were removed. The suggestion of Peck[11] to leave the ends of the intestine closed for some hours until adhesion takes place has been of great value on a number of occasions, and permits primary union of the operative wound.

Of 42 patients with diverticulitis, with and without carcinoma, on whom we have done resections, 14 per cent died as the result of the operation; that is, within four weeks. The mortality was high, but it must be taken into consideration that these patients were usually adipose, and it was often necessary to operate during the stage of obstruction, infection, etc. A large majority of the fatalities occurred in the earlier period, when it was believed that the tumefaction was due to carcinoma, and extensive dissections seemed to be indicated. It is of great value, therefore, to be able to differentiate between diverticulitis and carcinoma, as in diverticulitis the removal of the mass of tissue which would be essential in carcinoma is not necessary. When a primary resection was made, we employed an end-to-end union, but as a rule found it wise either to suture the anastomosed area well up into the peritoneum and leave the suture line exposed, or to pass a folded strip of rubber tissue entirely around the anastomosis to suspend it in the wound, as there was a tendency to late infections, and unless provision was made for drainage, slowly progressing peritonitis occasionally caused death. To provide against gas pressure we have sometimes passed a good-sized red rubber tube by way of the rectum entirely through and well above the anastomosed area and fastened it with a single suture to the anus.

In very extensive cases with obstruction, Balfour[12] advises making a complete ileostomy close to the cecum after the manner of Brown,[13] bringing the end of the ileum out through a small opening in the right side and closing its distal end completely, thus entirely diverting the intestinal contents from the large intestine. A cecostomy is made at the same time for cleansing the colon. This renders a resection of the involved colon much safer subsequently. Later, the end of the ileum is joined to the cecum end-to-side. A great advantage of this procedure is that the colon can be cleansed and maintained empty, and soon becomes nearly free from bacteria. Considerable experience with complete ileostomy in the management of ulceration of the colon has shown

that the patient maintains weight and excellent health, and that the disability is not at all so great as would be thought. After several weeks the stool becomes partly formed, is easily caught and contained in any one of the various colostomy bags, and there is much less odor than with a colostomy. I venture to say that, on the average, an ileostomy is much less of a nuisance than a colostomy.[14]

REFERENCES

1. Mayo, W. J.; Wilson, L. B., and Giffin, H. Z.: Acquired diverticulitis of the large intestine, Surg., Gynec. and Obst., 1907, v, 8–15.
2. Graser: Ueber multiple Darmdivertikel in der Flexura sigmoidea, Verhandl. d. deutsch. path. Gesellsch., 1899, Berlin, 1900, pp. 254–256.
3. Gordinier, H. C., and Sampson, J. A.: Diverticulitis (not Meckel's) causing intestinal obstruction, Jour. Am. Med. Assn., 1906, xlvi, 1585–1590. McGrath, B. F.: Intestinal diverticula: Their etiology and pathogenesis, with a review of twenty-seven cases, Surg., Gynec. and Obst., 1912, xv, 429–444.
4. Telling, W. H. M.: Acquired diverticula of the sigmoid flexure, considered especially in relation to secondary pathologic processes and their clinical symptoms, Lancet, 1908, i, 843–850, 928–931.
5. Brewer, G. E.: A consideration of the etiology of certain cases of left-sided intra-abdominal suppuration (acute diverticulitis), Tr. Am. Surg. Assn., 1907, xxv, 258–269.
6. Beer, E.: Some pathologic and clinical aspects of acquired (false) diverticula of the intestine, Am. Jour. Med. Sc., 1904, cxxviii, 135–145.
7. Plummer, S. C.: Technique of removal of tumors of the large intestine, causing obstruction, Surg., Gynec. and Obst., 1906, ii, 696–697.
8. Mayo, C. H.: Diverticula of the gastro-intestinal tract: Their surgical importance, Jour. Am. Med. Assn., 1912, lix, 260–264.
9. Giffin, H. Z.: Diverticulitis of the rectum, Ann. Surg., 1911, liii, 533–537; The diagnosis of diverticulitis of the large bowel, a clinical review of twenty-seven cases, Jour. Am. Med. Assn., 1912, lix, 864–866. Giffin, H. Z., and Wilson, L. B.: A case of carcinoma on diverticulitis of the sigmoid, Am. Jour. Med. Sc., 1909, cxxxvii, 661–666.
10. Wilson, L. B.: Diverticula of the lower bowel: Their development and relationship to carcinoma, Ann. Surg., 1911, liii, 223–231.
11. Peck, C. H.: Diverticulitis, Tr. New York Surg. Soc., 1910; Ann. Surg., 1910, lii, 264.
12. Balfour, D. C.: Meckel's diverticulum: A report of fifteen cases, Jour. Minnesota Med. Assn., 1911, xxxi, 110–112.
13. Brown, J. Y.: The Lane operation: The indications for and the limitations of the procedure, with a discussion of the principles underlying it, Tr. South. Surg. and Gynec. Assn., 1911, xxiv, 137–150.
14. Since completing this paper, I have read the following articles with great interest and profit:
    Drummond, H.: Sacculi of the large intestine, with special reference to their relations to the blood-vessels of the bowel-wall, Brit. Jour. Surg., 1917, iv, 407–413.
    Telling, W. H. M., and Gruner, O. C.: Acquired diverticula, diverticulitis and peridiverticulitis of the large intestine, Brit. Jour. Surg., 1917, iv, 486–530.

TRANSPERITONEAL SIGMOIDOTOMY FOR THE REMOVAL OF TUMORS IN THE MUCOUS MEMBRANE*

W. J. MAYO

The large intestine and rectum are prone to the development of tumors of an adenomatous, papillomatous, or fibrous character. Multiple adenomas, familiarly known as polyps of the rectum, multiple papillomas, or intestinal warts, and an infectious type in which small mucoid growths develop as the result of an inflammatory process in the mucous membrane, form well-defined clinical groups. On exploration, the entire large intestine and rectum will often be found involved. A considerable percentage of persons suffering from these inveterate disorders eventually develop malignancy. When seen early, the malignancy is usually found confined to a single growth, but later a large number of the growths undergo malignant change, probably because of the seeding of small transplants from the original focus. However, I have observed patients who have had polyposis of the large intestine for years without the development of malignancy.

As to the cause of polyposis and allied conditions, there seems to be no well-defined knowledge, but there is an impression that the polyps are the results of transplants carried up and down the intestinal tract by normal and reverse peristalsis from a single primary growth. The mucoid growths have an infectious origin. Many patients become extremely cachectic as a result of the hemorrhages and exhausting discharges caused by these growths. For relief it occasionally becomes necessary to do a colectomy as far as the lower sigmoid. Later, by means of a snare, the cautery, fulguration, or radium, the remaining growths are removed from the rectum and rectosigmoid. Soper has published an interesting report of a case of this description operated on by Bartlett.

In the frankly infectious cases which develop mucoid growths the infection will subside following an ileostomy (Brown) whereby the entire large intestine is put at rest for six months or more. Several patients have been cured in this way in our clinic, so that reimplantation of the ileum to the colon was not followed by a recurrence. Occasionally this method of treatment will prove efficacious and result in cure in polyposis. Therefore, before doing a colectomy, it is wise to do an ileostomy and wait some months to ascertain whether or not the polyps will disappear. In the meantime the rectum and lower sigmoid should be cleared of visible polyps, and the colectomy, if necessary, done as a secondary procedure. A complete ileostomy gives less annoyance than a colostomy; the stool soon becomes semisolid, is easily caught in a suitable container, and is nearly free from odor.

Localized polyposis, usually limited to one or two polyps of a fibrous character, is often found in the ampulla of the rectum. Such tumors become more and more pedunculated until they may be extruded from the anus with the stool and require replacement after each evacuation. A favorite seat of single polyps and localized papillomatous growths is in the lower sigmoid and rectosigmoid. When pedunculated, they can be removed through the sigmoidoscope by the cold wire. However, in this situation they are less frequently pedunculated, and may be completely sessile. Patients with such growths have blood, mucus, and purulent discharges from the rectum and a sense of uneasiness and gas in the lower sigmoid, signs and symptoms which call for careful sigmoidoscopic examination.

The condition of the lower sigmoid and rectosigmoid is, in a way, somewhat similar to that of the ampulla of the rectum in its relation to the sphincter. The rectum proper begins at the middle of the third sacral vertebra and is derived from the cloaca, a highly differentiated part of the hind gut. At the juncture of the sigmoid and rectum in most persons (Jonnesco) there is a marked change in the mucous membrane and a very considerable narrowing. Reeves, in a recent anatomic research on cadavers, found that this narrowing existed in 80 per cent and amounted to a constriction in 5 per cent.

Attempts to remove sessile tumors located in the lower sigmoid, through the sigmoidoscope, are not unattended with danger, and perforation with death from septic peritonitis as the result of such more or less blind procedures has been reported. We have found transperitoneal sigmoidotomy a simple, safe, and satisfactory procedure for the removal

of these tumors. A fragment from the growth, as exposed by the operation, may be removed for microscopic examination of the frozen section, so that operation may proceed more or less extensively as indicated. Such an examination is satisfactory provided a piece of tissue is secured which is representative of the structure of the growth. The
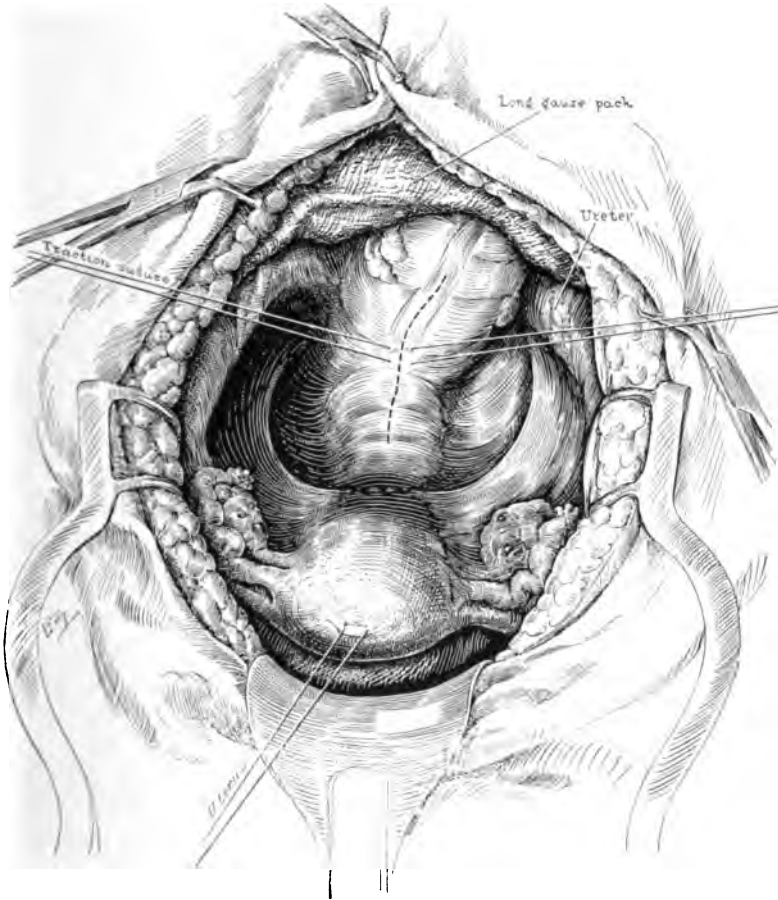

Fig. 53.—Exposure of lower sigmoid for removing tumor from within lumen. Dotted line shows proposed incision with traction sutures in place.

tearing off of fragments from a growth for examination admits of the possibility of infection of the growth itself, which may result in invasion of the blood-vessels and lymphatics by cancer, if this disease is present, and lead to metastasis in the liver or glands. I always regret the necessity for excising a section from a doubtful growth unless the entire growth can be immediately removed if malignancy is established. Under any

circumstances, the site from which the section was removed should be immediately sterilized with the cautery. It must be remembered, also, that unless the entire growth is given to the pathologist, a positive opinion is the only opinion of value; a negative opinion can be accepted only from an examination of the entire specimen.
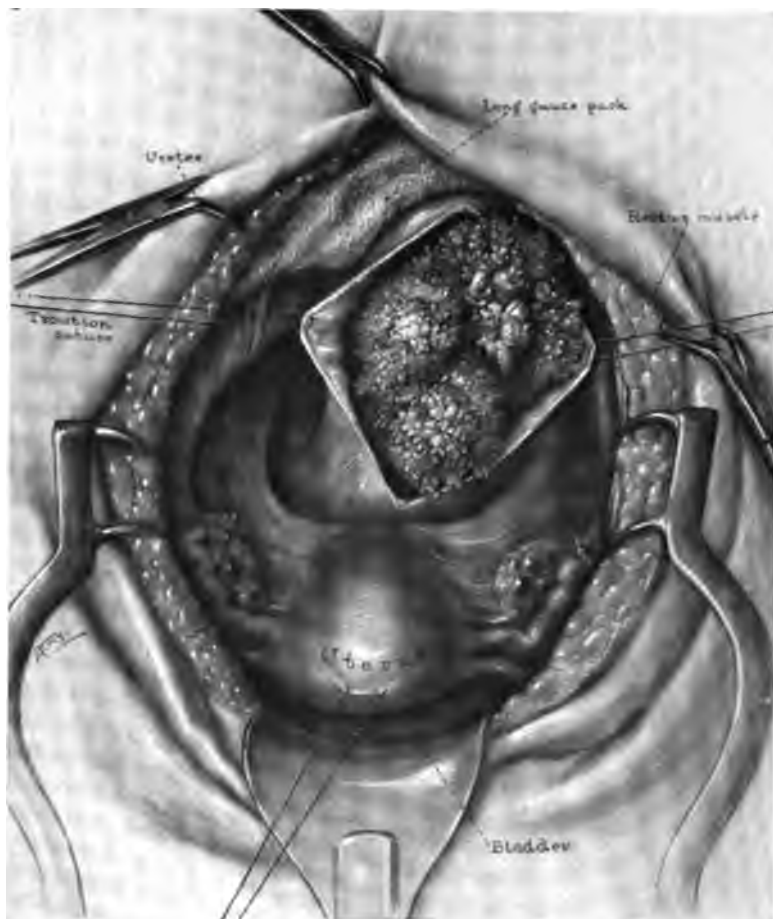
Fig. 54.—Papillomatous growth presenting through the opened sigmoid.

The technic for removing such growths by transperitoneal sigmoidotomy is quite simple, and the illustrations which were made by Miss Fry from a recent case require little comment. The abdomen is opened in the midline, suprapubically, and a Balfour self-retaining speculum adjusted (Fig. 53). A moderate Trendelenburg with a pack

gives good exposure. We now seldom use the exaggerated Trendelen-
burg, and in old and adipose persons we are especially cautious in this
respect. The sigmoid is opened on the anterior longitudinal band as
nearly opposite the tumor as possible (Fig. 54), and the tumor is ex-
posed, drawn through, and double clamped (Fig. 55). The growth is
removed with the cautery and the defect closed from the mucous side
by continuous sutures of chromic catgut after the method devised by

Fig. 55.—Clamps catching normal mucosa. Growth being burned off by cautery.
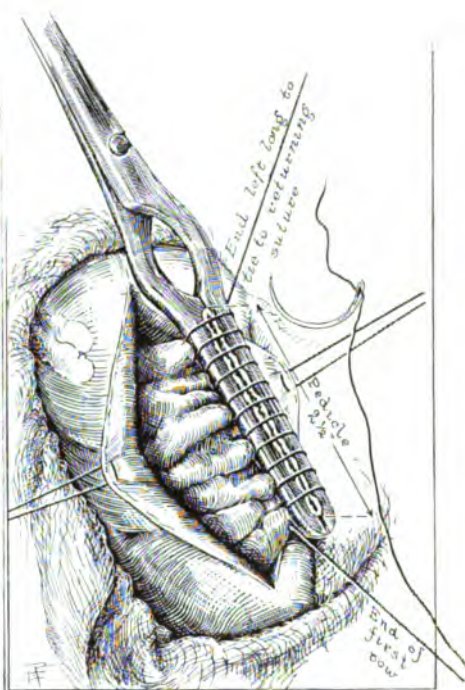
Fig. 56.—Continuous catgut suture placed around forceps, for closure of defect in mucosa (Pilcher method).

Pilcher for the excision of hemorrhoids (Fig. 56), and covered on the
peritoneal side with a few interrupted silk sutures. The incision in the
sigmoid is then closed with continuous catgut and interrupted fine silk
(Fig. 57). We then pass a red rubber tube up into the sigmoid beyond
the line of sutures and fasten it with a catgut suture to the anus; this
is left in situ for a few days to prevent gas pressure. We have never
applied this procedure to frank malignant growths, but for growths

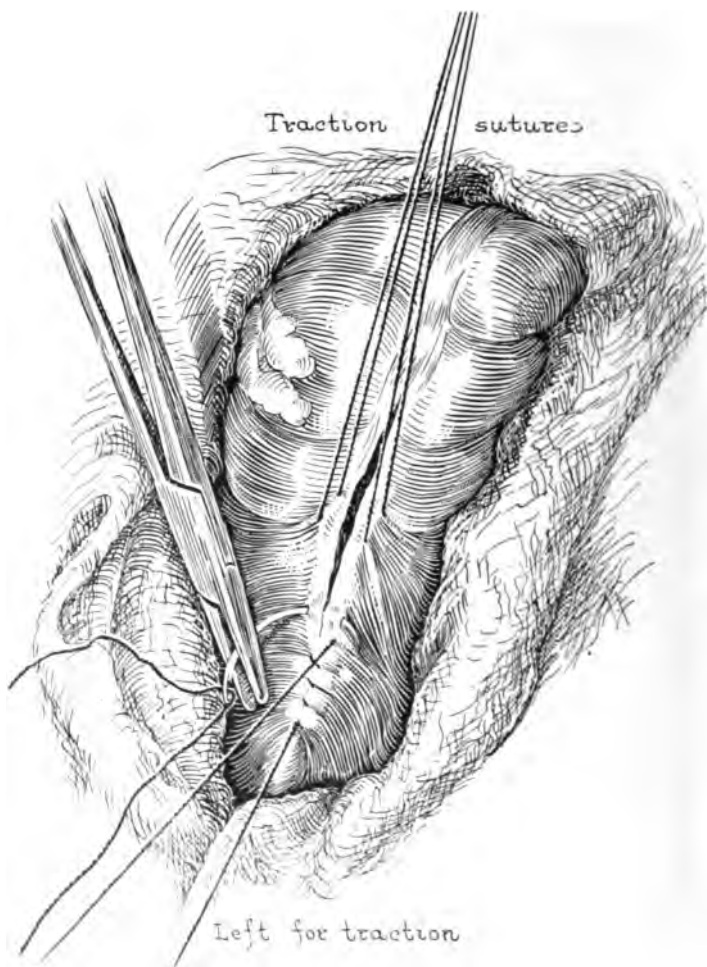similar to the papilloma shown in the drawings it will be found most efficient.

Fig. 57.—Closure of working incision in intestine.

REFERENCES

Brown, J. Y.: The value of complete physiological rest of the large bowel in the treatment of certain ulcerative and obstructive lesions of this organ, with description of operative technic and report of cases. Tr. South. Surg. and Gynec. Assn., 1912. xxv, 440–445.

Jonnesco: Table digestif. Poirier, P., Charpy, A.: Traité d'anatomie humaine. Ed. 2. Paris, 1901, vol. iv.

Pilcher, L. S.: Individual excision and suture in operating for the removal of hemorrhoids. Ann. Surg., 1906, xliv, 274–280.

Reeves, T. B.: Personal communication.

Soper, H. W.: Polyposis of the colon. Am. Jour. Med. Sc., 1916, cli, 405–409.

A STUDY OF THE RECTOSIGMOID*

W. J. MAYO

The rectosigmoid, the narrowest part of the large intestine, consists of 3.5 inches of the intestinal tract, which includes the terminal 2 inches of the sigmoid and the proximal 1.5 inches of the rectum. It is a definite mechanism which retards the fecal current and prevents continuous progress of the intestinal contents into the rectum. The examination of a large number of men for army service demonstrates that in the adult the normal rectum does not retain feces for any length of time, and when it does, such action is artificial and pathologic. With the exception of the pyloric end of the stomach and the first portion of the duodenum, the rectosigmoid is more frequently diseased than any corresponding portion of the gastro-intestinal tract.

In the older anatomies the terminal two inches of the sigmoid was often, if not usually, called the first portion of the rectum, because of certain anatomic peculiarities which rendered it difficult to say with certainty whether it was sigmoid or rectum. Following the researches of Treves and Jonnesco, it was definitely concluded that this portion of the intestinal tract was a part of the sigmoid and it is so designated in all of our later anatomies. The rectum proper begins at the middle of the third sacral vertebra and, anatomically speaking, ends at the level of the apex of the prostate in the male and at the upper level of the perineal body in the female, sites which mark the beginning of the so-called second portion of the rectum, or more correctly, the anal canal.

The anal canal of Symington has its origin in the proctodeum or skin infold. It is lined with pavement epithelium, has no mucous glands, and is in no way a part of the rectum, but is rather a retentive mechanism extraordinarily well adapted to temporary rectal retention. The anal canal is about 3 cm. in length, and passes upward and forward at such an angle in relation to the musculature of the rectum as to relieve

the strain on the sphincter muscles. This valve type of mechanism is exhibited in the compression of the ureter in the wall of the bladder and of the common duct in the wall of the duodenum. Its most important artificial imitation is shown in the brilliant work of Coffey which has made transplantation of the ureters to the large intestine an operation of safety and precision.

The rectum is, therefore, a single organ averaging 11 cm. in length, with a protective sigmoid mechanism above and the sphincter apparatus of the anal canal below. The upper of the two left valves of Houston, which is nearly always discernible although sometimes rudimentary, lies just below the inferior margin of the terminal sigmoid constriction. The lower left valve of Houston lies below the level of the peritoneum, while the single large right valve, which is nearly always present, projects well across the lumen of the rectum near the mid-point.

The ampulla of the rectum may be described as the sacculated portion lying between the anal canal and the lower left valve of Houston. The middle portion of the rectum ends above at the right valve, while the upper rectum extends to the sigmoid at the upper left valve. The index-finger of the average examining hand, when the anal canal is forcibly elevated, can reach to, and often a little above, the right valve of Houston, but not to the rectosigmoid juncture (Fig. 58).

This interpretation of the anatomy of the rectum is in harmony with its embryologic origin. The rectum proper is derived from the cloaca, a highly differentiated part of the hind gut, from which also the bladder is derived. Definite anatomic changes are to be found in the epithelial layers of the mucous membrane at the rectosigmoid juncture and possibly a tissue weakness worthy of note.

The terminal two inches of the sigmoid (Fig. 58) has considerable resemblance to the lower rectum just above the anal canal. The more or less circular folds of the mucous membrane of the sigmoid here take on a longitudinal arrangement with much the appearance of the columns of Morgagni and the rectal sinuses, and end in a rudimentary sphincter apparatus at the very beginning of the rectum. This hint of a sigmoid sphincter at the rectosigmoid union forms a well-marked resisting constriction to the readily dilatable sigmoid above and the rectum below (Jonnesco, Markel).

Examination shows that this circular band at the termination of the sigmoid contains considerable non-striated muscle-fiber (Figs. 58 and 59). Clinically, there is often seen through the proctoscope, when the

patient strains during examination, a tendency of the movable sigmoid to project through this muscle band as a slight intussusception into the fixed rectum. Tumors in the terminal sigmoid are not infrequently
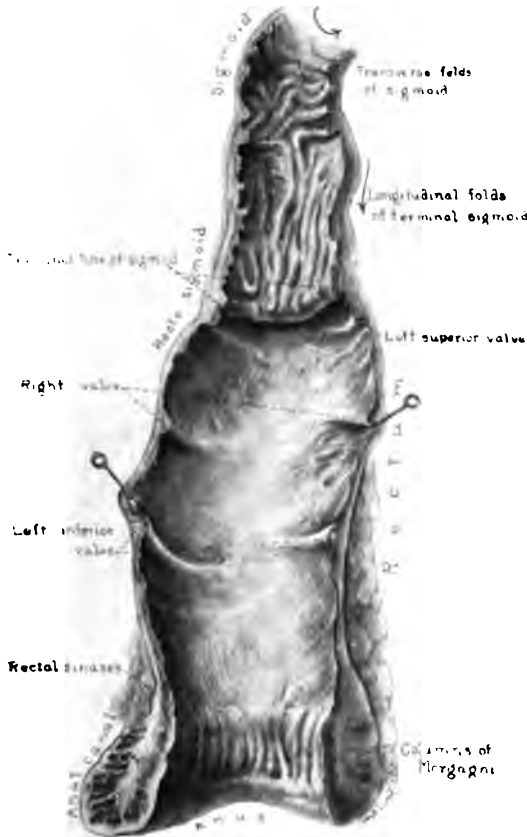

Fig. 58.—Terminal sigmoid, rectum, and anal canal from inside.

intussuscepted into the rectum, giving the diagnostician on digital examination the erroneous impression that they are rectal.

Through the kindness and with the aid of Dr. C. M. Jackson, head of the Department of Anatomy, University of Minnesota, Dr. T. B. Reeves, at my request, carefully dissected the rectum in 46 cadavers.

The terminal sigmoid constriction (Figs. 58 and 59) was found in 80 per cent, and in 2 of the 46 it amounted to a definite narrowing which reduced the caliber of the rectosigmoid juncture to a considerable extent. This narrowing seems to have attracted little attention from surgeons, and in the large majority of cases it is so slight as to be readily over-looked (Fig. 58). In addition, the anatomy was very carefully worked

Fig. 59.—Terminal sigmoid, rectum, and anal canal seen from behind, with relation to bony pelvis.

out in the cases presented for operation, and the drawings are the result of these combined studies.

Examination of the rectosigmoid, that is, the part of the rectum which lies above the right valve of Houston and the terminal two inches of the sigmoid from the inside, shows not only those definite changes in color and arrangement of the mucous membrane which characterize the rectum and sigmoid respectively, but also in a high percentage of

subjects the rudiments of the terminal sigmoid sphincter which defines the two organs. Examination of the outside of the rectosigmoid discloses prominent features of identification: (1) The rectum has no mesentery; (2) the longitudinal muscle bands of the sigmoid spread out, making a complete longitudinal layer for the rectum; (3) the superior rectal artery divides into the right and left branches at the origin of the rectum; and (4) the absence of epiploic tags, which are found on the sigmoid to its end (Fig. 59).

The impression is gained that ordinarily the rectosigmoid is an

Fig. 60.—The superficial anatomy of the sacral, coccygeal, and anal region. Note the notch which marks the line of bone section just below the fifth sacral foramina.

arrangement for retention of contents in the sigmoid proper, and that under certain circumstances the controlling mechanism may subject the parts to undue stress.

The rectosigmoid apparatus is controlled by the pelvic plexus of nerves which is made up of a variable number of sympathetic ganglia joined from above by spinal nerves from the lumbar region and from below by spinal nerves from the sacral region. From the lower part of the pelvic plexus nerves can be traced into the rectosigmoid region and the rectum. The inferior mesenteric plexus, containing a variable number of sympathetic ganglions, follows along the course of the superior

hemorrhoidal artery and helps to supply the rectosigmoid and the upper part of the rectum. According to Langley and others, the nerves derived through the hypogastric plexus are inhibitory in action, while those from the spinal and sacral nerves are motor (Fig. 61).

In addition to the nerves mentioned, the smooth muscle-fibers which compose the musculature of the rectosigmoid, like all non-striated muscle-fibers, have the power of originating contraction and, according to Keith, these impulses are collected in certain neuromuscular nodes
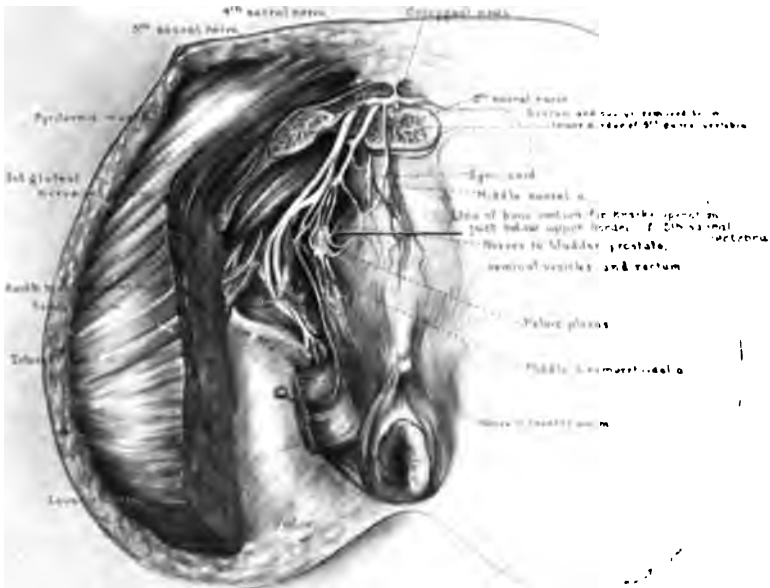
Fig. 61.—The deeper anatomy of the region shown in Fig. 60 as exposed by section through the third sacral vertebra as first advised for the Kraske operation. This line of section is liable to produce extensive injuries to important nerves and predisposes to sacral hernia. Line of section through the fifth sacral vertebra gives sufficient exposure and no important nerves are injured.

and correlated. Failure of coördination results in a most curious and interesting pathologic phenomenon: the so-called idiopathic dilatation of the colon, or Hirschsprung's disease. A number of cases of this condition have been recognized since the attention of American surgeons was called to it by Finney. The disease is similar in origin to cardiospasm at the cardiac orifice, pylorospasm, and stasis at the ileocecal valve.

The terminal sigmoid, as held by its mesentery, has considerable

play, and it curves from its rectal attachment. The longitudinal muscle bands are well developed and by spreading out grasp the entire rectum.   It is probable that contraction of these bands from the fixed point of the rectum under proper stimulation enables the sigmoid to straighten and pour its contents into the rectum, while under ordinary circumstances the angulation is co-effective in retention.   Investigation shows that the emptying of the large intestine from the splenic flexure is accomplished largely by siphonage.   The hardened head of the fecal
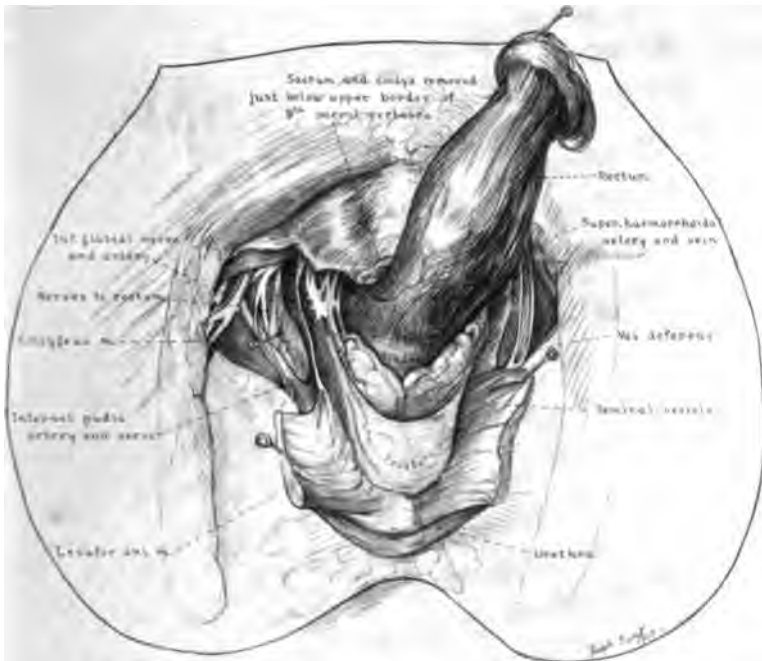
Fig. 62.—Anatomy anterior to rectum in the male, as seen in Kraske operation.

current rests at the rectosigmoid and the siphon is established when this mass, which can be compared to the piston of a syringe, moves onward.

From the foregoing it may be seen that the rectosigmoid is a distinct anatomic region which possesses some of the characteristics of the pylorus and of the ileocecal mechanism, and that it depends on its anatomic arrangement for function. The difficulty of guiding tubes and instruments from the rectum into the sigmoid is due to the recto-

sigmoid mechanism and makes futile the use of the so-called colonic tube in which the passage of a length of tube out of sight into the rectum, where it remains coiled, leads to the supposition that it has passed into the sigmoid. Single or several polyps which are so frequently found in the ampulla of the rectum and which, on straining, are grasped in the sphincter apparatus and rendered pedunculated, have their counterpart in the single, or at most, two or three polyps, which are so often found in the terminal sigmoid and which for the same reasons have become pedunculated into the rectum.

Experienced observers have called attention to the frequency of infections, polyps, diverticula, and various other pathologic conditions in the terminal sigmoid. With the exception of the pyloric end of the stomach, carcinoma is to be found more frequently in this 3.5 inches than in any corresponding part of the gastro-intestinal tract. In an investigation of the last 100 specimens of cancer of the rectum and rectosigmoid removed consecutively at St. Mary's Hospital, Rochester, Minnesota, it was found that 28 were located in the rectosigmoid juncture, extending as much onto the rectal as onto the sigmoid side, 21 involved the juncture, but extended more onto the rectal than onto the sigmoid side, 14 involved the juncture, but extended more onto the sigmoid than onto the rectal side. Thus 63 per cent involved the rectosigmoid, 30 per cent the rectum only, and 7 per cent the anal canal.

REFERENCES

1. Coffey, R. C.: Physiologic implantation of the severed ureter or common bile duct into the intestine. Jour. Am. Med. Assn., 1911, lvi, 397–403.
2. Finney, J. M. T.: Congenital idiopathic dilatation of the colon. Surg., Gynec. and Obst., 1908, vi, 624–643.
3. Jonnesco: Table digestif. In Poirier, P., and Charpy, A. Traité d'anatomie humaine. Paris: Battaille, 1901, vol. 4.
4. Keith, A.: A new theory of the causation of enterostasis. West London Med. Jour., 1915, xx, 149–162.
5. Langley, J. N., and Anderson, H. K.: Cited by Gaskell, W. H., in The Involuntary Nervous System. London, Longmans, 1916, pp. 43–44.
6. Markel, F.: Die pars ampullaris recti (Topographische Anatomie). Ergeb. d. Anat. u. Entwicklungsgesch., 1900, x, 583.
7. Symington: Cited by Cunningham, D. J., in Textbook of Anatomy, 2d ed., New York, Wood, 1905, p. 1085.
8. Treves and Jonnesco: Quoted by Cunningham, D. J., in Text-book of Anatomy, 2d ed., New York, Wood, 1905.

UROGENITAL ORGANS

RECENT OBSERVATIONS IN CYSTOSCOPIC TECHNIC*

W. F. BRAASCH

With the multiplication of various aids to the diagnosis of disease of the urinary tract there has been an increasing tendency to employ one and all of the methods without considering their individual necessity. As a result, many unfortunate complications have arisen which could have been obviated if greater care and better judgment had been exercised. The following rule should be adhered to as a guiding principle by every urologist; namely, make no manipulation in the urinary tract other than is necessary in order to complete a diagnosis.

We have grown to regard simple cystoscopy such a commonplace diagnostic procedure that we are apt to employ it when the clinical data are sufficient without it. There should be well-founded indications for cystoscopic examination. In the presence of a negative urinalysis and negative physical examination a cystoscopic examination should not be made merely because the patient complains of a slight degree of bladder irritability. Nor is an occasional pus-cell in the urine a sufficient reason for cystoscopic examination in the absence of other indications, since an occasional pus-cell or red blood-cell is frequently found in a passed specimen of urine when there is no lesion in the upper urinary tract. It is unnecessary to state that the finding of pus-cells in the urine of a female patient is of no value unless the urine is obtained by catheter. Cystoscopy should not be resorted to in order to identify every obscure abdominal pain unless the pain is associated with renal or vesical radiation. Neither is it necessary to resort to cystoscopy to identify every indefinite shadow in the roentgenogram unless supported by clinical indications. There are usually definite contraindications to any cystoscopic procedure: (1) When the patient is aged and infirm; (2) when the patient is in an emaciated and weakened condition; (3) when there is

bilateral renal involvement of extreme degree, and (4) when it is apparent that no surgical procedure would be of benefit.

Routine cystoscopic examination in every case of prostatic hypertrophy is unnecessary and may be followed by grave complications. I have known death to result on several occasions following cystoscopic examination in the presence of a very large prostate. In prostatic hypertrophy cystoscopy should be attempted only: (1) When on rectal examination the prostate is so small that it is questionable whether it could be the cause of urinary obstruction; (2) when the patient's symptoms are suggestive of a foreign body, tumor, diverticulum, or unilateral renal complication, and (3) when the roentgen ray shows shadows of a questionable nature. When the roentgen shadow is definitely the shadow of a large stone there is no need of cystoscopy to corroborate it.

When a cystoscopic examination is indicated in the presence of a large gland it is well to use a cystoscope of small caliber. Such an instrument should be used more frequently in routine cystoscopy of conditions other than hypertrophy. Many urethras are too small to permit of the passage of standard-sized cystoscopes without injury. A cystoscope of large caliber will frequently cause considerable bleeding and laceration of the urethra, and its use is often followed by severe forms of urethritis and prostatitis. I have observed several cases in which a stricture of the urethra followed cystoscopic injury. Although a cystoscope of small caliber usually permits only single ureteral catheterization, nevertheless a fairly complete examination can be made. When, on attempting cystoscopy, intolerable pain is caused, it is unwise to endeavor to complete the examination at one time. If the bladder is catheterized and irrigated daily over a period of ten days or two weeks, it is surprising how much more tolerant the patient becomes to instrumentation.

Severe reaction is occasionally seen following simple catheterization of the ureters. I have observed several patients who have been in bed as long as several weeks with chills and fever following simple catheterization of a kidney previously normal. Only recently, in a case in which a ureteral catheter was introduced into the pelvis of a supposedly well kidney (the other one being destroyed) and allowed to remain in the ureter for fifteen minutes while a differential functional test was made, there was subsequent acute exacerbation of a mild chronic pyelonephritis, uremia, and death. Although it is true that in a vast majority of cases there is no danger in renal catheterization, I have

repeatedly observed instances in which an infection occurred in the previously healthy kidney following catheterization when infection was present in the other kidney. When it is apparent that the patient's symptoms are caused by lesions in the bladder or urethra, it is not always necessary to catheterize both kidneys. When it is apparent that there is a unilateral surgical kidney, it is often unnecessary to catheterize the other kidney. However, should there be any doubt as to the functional value of the other kidney, and catheterization is necessary to ascertain this, the procedure is justified. Occasionally catheterization of the normal kidney may be obviated by the simple procedure of catheterizing the diseased kidney and making a differential functional test. The bladder specimen will then represent the functional activity of the non-catheterized kidney.

Considerable trauma and unnecessary pain may be caused by the use of a ureteral catheter of too large caliber. There is usually much less reaction following the use of a catheter of a caliber which permits it to be introduced without meeting much obstruction. The forcing of a large catheter, such as a No. 7 or even a No. 6, through a small meatus and up a small ureter with great pressure may be followed by considerable injury. When it is desired only to obtain a specimen from the kidney, a No. 5 catheter will suffice in the majority of instances. It is seldom necessary to use a catheter of larger caliber than No. 6 except in cases of ureteral dilatation.

Pilcher emphatically states that he considers pyelography a very dangerous procedure in the hands of any except the most expert, and that the method should be used only when a definite diagnosis cannot be made by any other means. In my opinion this is a timely warning and should be taken to heart by every one attempting to make a diagnosis of conditions in the urinary tract.

When the value of pyelography as an aid to diagnosis finally became recognized, it was employed generally. It was not long, however, before many cases were reported in which renal complications and even death followed its use. As a result of these dangers the method for diagnosis was in a fair way to be entirely discarded. An attempt was then made to discover some medium which would not cause injury to the kidney. Of the mediums proposed, thorium nitrate solution had many evident advantages over the others, and it was hoped that a medium for injection had been discovered which would meet all the ideal requirements.

Having used thorium extensively since its introduction almost two

years ago, I regret to state that while it has many practical advantages over the other mediums, it may be fully as harmful as colloidal-silver suspensions. When it has been retained in the pelvis of the kidney in hydronephrosis, it has occasionally been the cause of diffuse abscesses throughout the cortex similar to those seen with the use of colloidal-silver suspension. The only difference in the resulting lesion is that on microscopic examination no evidences of particles of undissolved silver are visible. The kidney tissue throughout appears markedly irritated and inflamed and the pelvic mucosa shows evidence of acute pyelitis. The microscopic evidence of infection and necrosis is to all appearances the result of irritation and infection ascending from the renal pelvis by way of the tubules. In a series of cases in which we endeavored to remove the injected thorium solution from the pelvis following pyelography, no necrosis resulted. It is advisable, therefore, following the injection of thorium when hydronephrosis is suspected, to leave the ureteral catheter in place so as to allow the fluid to drain away. This should be followed by repeated lavage with sterile water until every trace of the medium is removed. Unfortunately, this is not always possible because of retention in the ends of the dilated calyces. Dilatation of the renal pelvis may usually be recognized by other cystoscopic means than pyelography. Recognizing the possible danger resulting from retention of injected mediums, we should endeavor to make the diagnosis of hydronephrosis without resorting to pyelography, and its use should be confined to cases in which other methods of diagnosis leave us in doubt.

Since interference with the drainage of medium injected for pyelography is the cause of resulting damage, we have similar problems to meet in the diagnosis of roentgenographic shadows appearing in the ureteral area. In attempting to identify these shadows, I have on several occasions seen similar evidence of renal infection and cortical abscesses following ureteral pyelography, which could be relieved only by removal of the obstructing stone, and in one case required nephrectomy as well. It is obvious that it is fully as necessary to remove the injected medium completely in cases of stone obstruction as in cases of hydronephrosis.

In the majority of cases in which shadow interpretation is necessary, the evidence obtained by the cystoscope, the ureteral catheter, and the wax tip will suffice. When an impassable obstruction is met with, a shadowgraph catheter will usually be sufficient. However, when there

is a suspicious shadow in the original roentgenogram and the catheter meets with little or no obstruction, pyelo-ureterography may be employed to great advantage, and is frequently the only method by which an exact diagnosis can be made. Such conditions will permit of thorough drainage and evacuation of the injected medium.

Because of possible retention of the injected medium, it is obvious that simultaneous bilateral pyelography is never justifiable. Furthermore, before a pyelogram is made, we should be reasonably certain that the other kidney is normal. Unilateral pyelography with bilateral lesions, such as nephrolithiasis, polycystic kidney, and fused or horseshoe kidney, is attended with greater danger than when the lesions are unilateral and should be attempted only when the indications are urgent. When a horseshoe kidney is suspected, the relative position of the kidney and pelvis can usually be ascertained by means of a shadowgraph catheter. If further complicating pathology is suspected, pyelography can be resorted to later if necessary. Although it has been said, and with truth, that when complications follow pyelography the kidney is usually otherwise surgical, occasionally a moderately diseased kidney suffers such injury following pyelography that nephrectomy is necessary.

Cystopyelography is also not without its dangers, although it is true that none of the bladder medium will gravitate to the kidney unless there is free access through a dilated ureter. In two instances in which the medium had entered the kidney by gravity from the bladder it was subsequently impossible to drain from the dilated calyces present. As a result, the patients suffered severe reaction, and, after a prolonged convalescence, their renal function was considerably impaired.

The diagnosis of hydronephrosis may be arrived at usually by other means than pyelography: (1) By the determination of residual urine in the pelvis; (2) by overdistention, and (3) by withdrawal of retained fluid through a syringe. When the ureteral catheter had been introduced into the dilated pelvis, the retained urine will run out in a continuous stream without peristaltic hesitation. This can usually be quickened and slowed at will by manual pressure over the kidney area. Continuous rapid flow from a ureteral catheter without peristalsis may occur, however, when there is nervous hypersecretion in kidneys otherwise normal. Such hypersecretion is always bilateral and, therefore, can be differentiated from the unilateral rapid excretion from the dilated renal pelvis.

The well-known overdistention method of Kelly has proved invaluable in the diagnosis of hydronephrosis. Although there has been some dispute as to the capacity of the normal pelvis, it is now generally recognized that when any amount greater than 15 c.c. can be injected without causing pain, dilatation is suggested. This does not, however, necessarily signify that the pelvis itself has a capacity of 15 c.c. The injection of 15 or even 20 c.c. of fluid before pain results is possible with an actual pelvic capacity much less, since part of the injected fluid may return along the side of the catheter to variable distances down the ureter. Therefore, the amount injected in such a case represents the capacity of the pelvis and a part of the ureter as well. This may be proved by injecting an opaque fluid: the partial return flow will be evident in the pyelo-ureterogram.

My experience with the last-named test, the withdrawal of residual urine, has brought out several points of interest. It is evident that if there are several ounces of retained fluid in a dilated pelvis, it may usually be withdrawn through the ureteral catheter by means of a syringe. On several occasions, however, I have noticed an interesting phenomenon, i. e., that similar suction will withdraw several ounces of fluid from a kidney with a pelvis of normal size. This occurs, however, only when there is a condition of excessive hypersecretion. It is necessary that the ureteral catheter should fill the ureteral lumen so that suction with the syringe establishes a lower intra-ureteral pressure. It would appear that the process is one of glomerular infiltration and is dependent on the difference in intrarenal pressure. A large amount of fluid withdrawn from a hypersecreting kidney may be differentiated from residual urine by the fact that when a hydronephrosis is present, the amount withdrawn can be injected back into the kidney pelvis without causing pain, whereas in normal hypersecreting kidneys if an ounce of urine is withdrawn, renal colic will usually be caused by reinjecting 5 or 10 c.c.

In conclusion, I would say that pyelography should not be used when the diagnosis can be made without it. Even though the diagnosis remains in doubt, pyelography should not be attempted if the patient is old and feeble, or weak and emaciated, or if the condition of the other kidney is not normal. When clinical conditions are favorable, however, and a pyelogram is made, it is advisable to leave the catheter in the ureter for at least fifteen minutes so that it may drain thoroughly. The pelvis of the kidney should then be irrigated repeatedly with sterile water. The patient should be kept under close observation and if there

is evidence of marked pelvic retention the kidney should again be catheterized within twenty-four hours, the ureteral catheter allowed to drain for several hours, and the pelvis again irrigated. If the patient does not recover following this procedure, a nephrectomy should be done without further delay. By a careful selection of cases and the use of all the technical precautions, the percentage of injury will be reduced to a minimum. Pyelography is of too great value to be discarded, for a number of conditions cannot be diagnosed without it. However, it is obvious that the method should not be employed by one who has not had considerable cystoscopic experience and who has not the facilities to observe the patient carefully during and after examination.

REFERENCE

Pilcher, P. M.: Practical cystoscopy, Philadelphia, Saunders, 1911, p. 157.

TUMORS OF THE BLADDER AND THEIR NON-OPERATIVE TREATMENT*

W. F. BRAASCH

When the method of removing bladder tumors through the cysto-scope by means of a high-frequency current was first introduced by Beer, it was believed that a method had been discovered whereby all such tumors could be effectively cured. It gradually became apparent, how-ever, that certain types of bladder tumor could be readily removed by this method, while others were affected but little by it. It is now recog-nized that fulguration is applicable only to tumors of the papillomatous type.

The exact pathologic status of a papillomatous tumor of the bladder may be difficult to establish definitely. All papillomas are potentially malignant. Clinically, however, the grade of malignancy varies widely. It is generally recognized that such growths as are characterized by a uniform arrangement of cells and staining qualities, and are well confined within the basement membrane, are of relatively benign type. Never-theless such tumors, when removed, frequently recur and may later change to a more malignant form. It has also been established that papillomatous tumors with an irregular arrangement of cells and stain-ing qualities, and such as infiltrate the tissues beyond the basement-membrane, are distinctly malignant in type, and when removed, have a tendency to rapidly recur and metastasize. Between these two ex-tremes of papillomatous tumors, various grades of irregularity in forma-tion and staining qualities of cells may be observed, and it may be diffi-cult, from the pathologic picture, to determine the future clinical course. It is, however, often difficult to ascertain the exact microscopic character of a papillomatous tumor from specimens removed through the cysto-scope, since the outline, staining qualities, and arrangement of cells may vary in different portions of the tumor.

As a rule, a satisfactory diagnosis of the nature of a papillomatous tumor can be made by its gross appearance as seen through the cystoscope, together with clinical data. The cystoscopic data which differentiate the malignant from the relatively benign papillomatous tumor are:

1. A tendency to necrosis* and incrustation of the superficial portions, giving it a dirty gray appearance.

2. A heavy, meaty appearance, with a thick pedicle, in contrast to the frail structure of a benign papilloma.

3. The frequent presence of an intractable and very irritating cystitis.

Valuable data may be obtained by simple rectal and vaginal palpation, which should be done in every case of suspected tumor of the bladder. A malignant tumor involving the base of the bladder will frequently cause palpable thickening of the bladder-wall. When the process has progressed so as to cause a firm, nodular change in the adherent tissues, any operative procedure is useless. It is obvious that no benign tumor could cause such infiltration, and when the latter is present, fulguration would be futile.

It has been found that papillomatous tumors, regarded as relatively benign on microscopic examination, are readily removed by fulguration through the cystoscope, while tumors regarded as frankly malignant, on microscopic examination will not react to fulguration. Such tumors as fall in between these two groups may or may not react to fulguration. In the group of papillomatous tumors, when any doubt may exist as to their malignancy, the best method to ascertain the degree of malignancy is through their reaction to fulguration. If a tumor does not respond to three or four such treatments, it may readily be concluded that it is of the malignant type and that a suprapubic resection should be done without delay.

Several patients have come under our observation in the past few years who had previously been subjected to repeated fulgurations—in the case of one as high as 20—without affecting the bladder tumor. This is particularly unfortunate, since a tumor originally amenable to operation may become inoperable after the long delay and ineffectual treatment.

Now that the type of tumor which may be destroyed by fulguration has been definitely established, the question arises: How permanent are

* Albarran, J.: Les tumeurs de la vessie. Paris, Steinheil, 1892, 494 p.

the results of the removal of tumors by means of this method? On reviewing our records we find that there were 80 cases of bladder tumor fulgurated at the Mayo Clinic between January 1, 1911, and September 1, 1917. Of this number 50 were relatively benign papilloma, 9 were papilloma of questionable malignancy, 13 were carcinoma, 1 was angioma, and 7 were questionable papilloma. The Oudin current was employed in the earlier cases, but more recently the d'Arsonval current has been used because of its more rapid results.

Of the 50 patients with benign tumor treated, 33 have been reëxamined. No evidence of recurrence was noted in 24 patients, who were examined three or more months following fulguration, while 9 had recurrences. Of the 24 patients having no recurrence, the period following the initial treatment was as follows: 2 six years, 2 four years, 1 two and one-half years, 2 two years, 2 one and one-half years, 3 one year, and 12 less than one year. This leaves 24 of 33 patients (73 per cent) with benign papilloma who have been reëxamined, without any evidence of recurrence. It is probable that this percentage will be reduced by subsequent recurrence among the patients treated within the last year or two. Of the 9 patients with recurrence there were 4 who had a recurrence of the tumor following the first fulguration, but who, on recent examination, were found well over periods of from one to four years. In the 5 patients showing a recurrence at the time of the last examination the interval following fulguration was as follows: 2 four months, 1 six months, 1 six months and subsequently eight months, and 1 has had three yearly recurrences.

The site of recurrence was found at the original site of the primary tumor in 6 cases and at different sites in 3. The exact time of recurrence was difficult to ascertain because of the irregularity of examination following fulguration. However, of the 9 patients with recurrence it was noted in 8 in less than six months. In the one patient in whom the recurrence was repeated it was observed one and one-half years following fulguration. No recurrences were noted in cases in which the primary tumor was removed by one or two fulgurations. This is corroboratory of a previous observation that the degree of malignancy is in direct proportion to the number of fulgurations necessary to its removal. Keyes claims that recurrence will usually take place within three months. Of the 3 patients with primary multiple tumors reëxamined, 2 had multiple recurrences, which would corroborate Keyes' statement that recurrences following the fulguration of multiple tumors are multiple. Multiple re-

currence was also noted in one patient with primary single tumor. A second recurrence was observed in but two patients, and the primary tumor was multiple in both. Repeated recurrences usually occur with multiple primary tumors.

Of the remaining 17 patients who were not reëxamined, 5 were reported as symptomatically well and no subsequent data were available from 12. Of the patients reported well, the period following the last treatment was as follows: 1 six and one-half years, 1 six years, 1 five years, 1 two and one-half years, 1 two years. Of the 12 patients without subsequent report, 8 were fulgurated within the past year. While it is difficult to draw exact conclusions as to recurrences from this group without having made a cystoscopic reëxamination, nevertheless it is significant that 5 patients are reported alive and well from two to six years after fulguration. It is also of interest that there remain but 4 patients who have not been heard from. It is fair to assume that the majority of these are still living.

Of the 9 patients with papilloma of doubtful malignancy, 4 were fulgurated without success and, later, resection was done. Of the remaining 5, 1 was well two years and 1 six months afterward, 1 had multiple recurrences annually, 1 showed extensive recurrence five months later, and 1 was treated three months previously. An interesting occurrence was that of two tumors in the same bladder; one was relatively benign ' and was readily removed by fulguration; the other was not affected by fulguration, and on resection later was found to be malignant. It is evident that although a few cases of malignant papilloma will respond to fulguration, the majority will not.

Of the 13 patients with carcinoma, in 9 the treatment was given for recurrences following suprapubic resection for carcinoma. In 4 patients the tumors were of a doubtful nature on clinical examination, but did not respond readily to fulguration, and were operated on later. Of the 9 patients that were fulgurated following operation, 1 was fulgurated after fifteen months, and has been well for two years, 1 was fulgurated after two years, and has been well four years, 1 was fulgurated after eighteen months, and in a letter from the patient three years later he states that he is well, 1 was fulgurated after three years and has not been seen for three months, 1 has been fulgurated yearly for the past three years for recurrences, and was last examined five months ago, and 1 was fulgurated three months after operation and has not been examined for three months. Three of the patients have died from one to two years

after operation. It will be noted that the period of freedom from re-
currence was much longer after fulguration than after operation. The
time of recurrence following fulguration was more than a year in all but
two patients, and much longer than that observed with relatively benign
papilloma. Tumors which have been frankly malignant at operation
will frequently respond to fulguration when they recur. The degree of
malignancy is evidently reduced with successive recurrences, and even
though the patient may not be cured, life is unquestionably prolonged.

In the 9 cases of recurrence in this group, 5 were at the previous site
of the tumor and 4 were at different sites. In 3 cases the recurrence was
multiple and in 3 single. Cystoscopic examination several months after
resection for a malignant tumor will occasionally reveal evident prolifera-
tion of the mucosa at the site of the previous incision. There may be no
evidence of other involvement of the external wound, but this prolifera-
tion may persist and remain stationary for many months. It is advis-
able, however, to give it a thorough course of fulguration and radium
exposure.

In the 7 cases of questionable papilloma the time since the last ful-
guration is as follows: 1 six years, 1 five years, 1 four years, 1 three years,
2 one and one-half years, and 1 less than a year. None of these patients
have been reëxamined, but letters received from them indicate that there
is no recurrence.

Papillomatous proliferation of the mucosa to a slight degree, the
exact nature of which it is difficult to determine, is sometimes visible in
the bladder. Such tumors are found more often near the ureteral mea-
tuses or the internal vesical sphincter, and although they are probably
the result of a slight chronic inflammatory reaction of the mucosa, no
other evidence of inflammation may be visible. They may disappear
spontaneously, but they will occasionally remain stationary in size for a
period of several years. It is quite possible that some of these are the
forerunners of papillomas or malignant tumors, which is further sug-
gested by the frequency with which malignant tumors are found near the
ureteral meatuses. Such tumors, when discovered, should be removed
at once by fulguration.

Severe chronic inflammation will occasionally cause such extensive
proliferation of the mucosa that it may simulate a true bladder tumor.
This is particularly true with vesical tuberculosis. Microscopic exami-
nation of the tissue in question or catheterization of the kidneys would
usually identify the lesion. The specimen obtained, however, may be

unsatisfactory, and renal catheterization may be impossible, thus making identification of the tumor exceedingly difficult.

The number of treatments necessary to remove tumors is not always in ratio to their size. Occasionally tumors of considerable size are removed in one fulguration, whereas much smaller ones may require several treatments. It would seem that the rapidity with which the tumors disappear is in a measure in proportion to the degree of malignancy. The treatment of large tumors may be hastened by the preliminary removal of much of the tissue by means of a snare, as suggested by Buerger.

Following the removal of a papilloma by fulguration there will usually be considerable inflammatory reaction in the mucosa, and consequent edema and granulation tissue may simulate a persistent remnant of the papilloma. This, however, will gradually disappear spontaneously in the course of three or four weeks. Occasionally the bladder mucosa at the site of the suprapubic incision remains congested and irregularly infiltrated for a long time following fulguration, and such congestion, when persistent, is frequently indicative of underlying malignancy. Thorough fulguration of the area should be tried, and if the congestion still remains, radium should be used.

Radium.—Since radium has been used with such good results in treating superficial malignant conditions, such as in the skin, larynx, etc., it would be reasonable to expect similar results in the bladder. Thus far, however, the experiences reported have not been encouraging. Geraghty believes that it is of little or no value in the treatment of frankly malignant tumors of the bladder. His method of application consisted of hourly exposures with 100 mg. of radium, screened by a brass capsule 3 mm. in thickness, which is applied directly over the tumor by rigid instruments within the bladder. He reports a series of papillomatous tumors, however, that did not respond to fulguration until they had been exposed to radium. After this they were readily removed by fulguration. Berringer, on the other hand, reported evident cures with radium alone in 3 of 9 cases of inoperable malignant tumors. His technic differs from that of Geraghty in that the unshielded original lead capsule of radium is inserted in the bladder and the patient placed in a position to bring the capsule in contact with the tumor. It is further allowed to remain in the bladder for a much longer time, namely, five or six hours. Kolischer[*] reported successful removal of several malignant tumors with

[*] Kolischer, G.: Radiotherapy and diathermy in malignant tumors of the bladder. Urol. and Cutaneous Rev., 1916, xx, 66–67.

the use of mesothorium. He employs this intravesically, leaving the capsule in the bladder as long as twenty-four hours.

Our experience with radium has been largely as an aid to post-operative and preoperative treatment. Following resection of malignant tumors, it has been our custom to leave the unshielded radium capsule in the bladder for several hours in the hope of destroying any superficial malignant cells remaining. In preoperative and inoperable conditions it has been found valuable in reducing infection and cleaning up foul-smelling urine. In cases of persistent bleeding from the tumor a few hours of exposure to radium will often control it. This, together with deep x-ray exposure, is occasionally of value in controlling pain, sometimes found in inoperable cases. In 2 cases in which there was secondary recurrence of papillary carcinoma the tumor disappeared following long intravesical application of 100 mg. of radium. In 3 cases of secondary recurrence of the tumor in the suprapubic wound following resection, the nodules were softened and to all appearances the process was temporarily controlled. It may be said, therefore, that although radium does not have the brilliant therapeutic results of fulguration in the treatment of bladder tumors, it is nevertheless a valuable adjunct when the condition is malignant.

In summarizing our experiences with the non-operative treatment of tumors of the bladder it may be said:

1. Fulguration offers a safe and comparatively easy method of removing bladder papillomas.

2. Fulguration is applicable only to the papillomatous tumors of a relatively benign type.

3. Although the ultimate results following fulguration are much superior to those following suprapubic resection, the method does not always offer a permanent cure.

4. The degree of malignancy is usually readily ascertained by the cystoscopic appearance and clinical data.

5. In doubtful cases the degree of malignancy is best ascertained by its reaction to fulguration.

6. The percentage of recurrence of papillomas in a series of 33 cases repeatedly reëxamined was 27.

7. Recurrence when present usually occurs within six months after fulguration and is generally at the site of the primary tumor.

8. Multiple recurrence is more often observed with multiple primary tumors.

9. Tumors which have been frankly malignant at operation will frequently respond to fulguration when they recur.

10. The degree of malignancy is evidently reduced by successive recurrences.

11. Small papillomas usually situated near ureteral meatuses are occasionally accidentally discovered. While some are inflammatory, others are forerunners of large papillomas and should be fulgurated.

12. Radium is of value—(1) As a prophylactic measure following surgical resection of bladder tumors; (2) to control hematuria and pain; (3) occasionally in removal of malignant tumors, particularly when recurring.

LITHIASIS WITH BILATERAL RENAL INVOLVE-MENT*

W. F. BRAASCH

When lithiasis is found to exist with bilateral renal involvement, certain problems of diagnosis, prognosis, and treatment arise which merit special consideration. The various conditions in which such involvement is present may be as follows:

1. Bilateral nephrolithiasis, including stone in the ureter on one or both sides.

2. Lithiasis in one kidney and disease in the other.

3. Lithiasis in a solitary kidney.

4. Lithiasis in a fused kidney.

BILATERAL NEPHROLITHIASIS

On reviewing the records of the Mayo Clinic from January 1, 1910, to October 1, 1917, it was found that 62 patients had been operated on for bilateral nephrolithiasis. During the same time 504 patients with unilateral lithiasis were operated on, making a percentage of 12.3 of bilateral lithiasis occurring in the operative cases. It is, however, difficult to determine the exact proportion in which bilateral nephrolithiasis occurs, because of the many associated factors. It would be necessary to include: (1) All cases of bilateral nephrolithiasis and uretero-lithiasis which for various reasons were not operated on; (2) cases of ureteral stones on the opposite side previously removed by operation and cystoscopic manipulation, since they are in fact dislodged renal stones, and (3) all stones passed spontaneously from one or both kidneys and ureters.

General statistics.—In the series of 62 patients operated on there were 40 males and 22 females, which is in keeping with the relative occurrence of sex, as noted in cases of unilateral lithiasis. It is of interest that

lithiasis should occur practically twice as often in the male as in the female. This relative proportion also holds good in other forms of chronic renal infection, and is suggestive of the infectious etiology of the condition. The average age of the patients was forty years, and the average duration of symptoms was nine years. It is unfortunate that the symptoms associated with lithiasis should be allowed to remain without treatment during so long a period. Their long duration is in a large measure responsible for the comparatively poor prognosis and the various complications so frequently seen with bilateral lithiasis.

Localization of pain.—The pain was localized definitely to both sides in only 14 cases, to one side in 26 cases, and in 14 cases to one side recently, with a previous history of more or less definite pain on the other side. Renal pain was absent in 8 cases. The large number in which the pain was entirely or predominating on one side (64.51 per cent) should emphasize the necessity of making a complete roentgenographic exposure of the kidneys and ureters on both sides in every case. In cases in which the pain was absent, attention was called to the possibility of nephrolithiasis by the presence of microscopic pus in the urine. In the majority of instances the kidney causing the most pain, particularly in recent years, was found at operation to be the better of the two. The kidney which in former years had caused most of the pain, with little or no pain recently, was, in the majority of instances, largely destroyed, and a nephrectomy was necessary.

Location of stones.—The location of the stones in cases in which both sides were operated on, was, pelvis and calyces, bilateral, 10; pelvis and calyces on one side and cortex on the other, 7; pelvis and calyces on one side (nephrectomy on the other), 7; cortex on one side (nephrectomy on the other), 9. When one side only was operated on the stones were found located as follows: pelvis and calyces, 14; cortex, 6. There were 7 nephrectomies and 2 negative explorations. No attempt was made to localize the stones in the cases of pyonephrosis with stones, since the destruction of the kidney-tissue was so great that it was impossible to determine their exact situation. It is evident that in cases of bilateral nephrolithiasis the majority of stones are situated in the pelvis and calyces, as in cases of unilateral stones. Literature on the subject would lead us to believe that stones are most commonly situated in the cortex in cases of bilateral lithiasis. Many cortical stones described as such in the operation records were probably situated originally at the end of the calyces.

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Estimation of renal function.—Estimation of the combined renal function may, in a few cases, be of considerable aid to prognosis. Phenolsulphonephthalein is, for all practical purposes, as valuable as any functional test. When the return in two hours is only a trace or persistently very low, the prognosis is necessarily grave, and operation is usually not advisable unless there are urgent indications. We have, however, observed two patients in whom there was a persistent low phenolsulphonephthalein output, 5 and 8 per cent respectively, several years after operation. When the phenolsulphonephthalein return is moderately low, varying from 20 per cent to 40 per cent, I have frequently observed that it will later become much higher following operation. This is particularly true in the presence of marked infection relieved by drainage subsequent to lithotomy, and it may be inferred that toxic absorption as well as reflex irritation may be the cause of temporarily reducing the renal activity. A high return—50 per cent or more—is of value when clinical symptoms, or the general appearance of the patient, is suggestive of renal insufficiency. Particularly is this true in the presence of marked renal infection with toxic absorption, which frequently causes symptoms simulating advanced renal insufficiency. A high phenolsulphonephthalein return would assure the existence of one good kidney at least. The combined functional test, therefore, is of practical value only with a normal or extremely low return where the clinical appearance is doubtful.

It may be desirable to determine the comparative degree of function remaining in the two kidneys. This is not always possible, but frequently may be done—(1) by the size and character of the stone; (2) by cystoscopic inspection; and (3) by a differential functional test.

Radiographic data.—Very large stones, and more particularly large branched stones, will, as a rule, cause so much tissue-destruction that nephrectomy will be necessary. Occasionally, however, the amount of secreting tissue remaining is surprising in spite of the existence of large branched stones. The difficulties in removing such stones entirely, particularly when soft and crumbling, without too much damage to the kidney-tissue, are considerable. Single round stones, even though of large size, may cause comparatively little damage to the kidney-substance, and usually offer a better prognosis. Multiple stones, particularly when of large size and scattered throughout the kidney, usually indicate complete destruction of the kidney.

Cystoscopic inspection.—Such inspection may be sufficient to de-

termine the comparative functional ability.   If thick pus is seen exuding occasionally, or only on pressure, the destruction of the kidney may be taken as very evident, and ureteral catheterization will be unnecessary. When, however, the urine on one or both sides is clear or only moderately cloudy, a differential functional test may be of some value.   As I have previously stated, pyelography may give more accurate data as to the extent of renal destruction than any other method.   When the pelvis and calyces are seen to be markedly dilated and irregular, it may be inferred that comparatively little healthy tissue remains.   Pyelography should, however, be employed only when other methods fail, and then only when a comparative estimate of renal function is of practical value.

   Differential functional test.—The irritation caused by stone in the kidney will usually interfere greatly with the accuracy of the estimate of renal function.   It is difficult to explain the variable degree of reflex inhibition of secretion exerted by renal stone.   One kidney containing a stone may have a phenolsulphonephthalein return of but 4 or 5 per cent in fifteen minutes, while another, with a stone similar in size and position and with the same degree of infection, may have a normal return.   As a rule, small stones of recent origin and without marked infection will cause comparatively little functional disturbance.   Low functional return in the presence of stone is usually succeeded by a normal phenol-sulphonephthalein output after the stone has been removed.   Renal functional tests can only give us an estimate of the functional activity of the kidney at the time of the examination, and not what the kidney is capable of doing under normal conditions.   Too much reliance cannot, therefore, be placed on the amount of normal tissue in the kidney, as shown by the phenolsulphonephthalein test.   This was well illustrated in one of our recent cases with stone in the left renal pelvis, in which the differential phenolsulphonephthalein estimate from the left kidney was 7 per cent in fifteen minutes.   From this it might be inferred that considerable healthy tissue remained and a conservative operation would be indicated.   At operation, however, a large abscess was found in one pole, together with several soft areas in other portions, so that a nephrectomy was clearly necessary.   In several other instances in which branched stones were present the phenol-sulphonephthalein return was surprisingly good, and on surgical exploration the kidney was found to be so markedly diseased in areas that a nephrectomy was obviously indicated.   On the other hand, if the phenolsulphonephthalein return is zero or only a trace, it may usually

be inferred that the kidney is so largely destroyed that a nephrectomy is indicated. If, however, the phenolsulphonephthalein test is only comparatively low, the functional test is of uncertain value, and unless the other data obtained by physical, cystoscopic, or roentgenoscopic examination are of definite value, surgical exploration only will determine whether or not the kidney can be saved.

Indications for operation.—After it has been decided that an operation is advisable, the question arises: Which of the two kidneys should be operated on first? Rules as follows may be made:

1. In the presence of recent acute pain, repeated and continuous hemorrhage or toxic absorption from advanced renal infection referred to one kidney, that kidney must necessarily be operated on first.

2. If conditions do not necessitate this operation, the kidney with the better function should be operated on first, in order to take advantage of the function remaining in the kidney on the other side during the acute stages following operation. This is particularly imperative when the stone is so situated that the drainage from the kidney with the better function may be obstructed. When the irritation, infection, and danger of obstruction have been removed by the lithotomy, the other kidney may be operated on and removed if it seems advisable.

3. In cases in which the patient is in excellent physical condition, and the stones are of moderate size and advantageously situated, the renal function only slightly reduced, and but little or no infection present, both stones may be removed at the same time.

Patients not operated on.—There were 33 cases in which a very evident diagnosis of bilateral nephrolithiasis was made, and the patients were not operated on. No operation was advised, for various reasons, in 21 cases, and in 9 operation was advised, but the patients did not return. Two patients were operated on for coincident malignancy in other parts of the body, and in one case the patient is awaiting operation.

Of the patients regarded as inoperable, the predominating symptoms in 9 were those of renal insufficiency. The history of pain was either entirely absent or of secondary importance. Our attention was called to the possibility of renal lithiasis by the presence of pus in the urine. It was found necessary to make a roentgenogram in every case in which there was pus in the urine, even if there had been no history of pain. While this necessitated a large number of negative x-ray exposures, nevertheless the frequency with which lithiasis was thus discovered made the procedure worth while. The renal insufficiency is usually the result

of long-standing infection. Of particular interest is the fact that five patients in this group complained primarily of gastric symptoms which were frequently the only subjective evidence of renal insufficiency to be noted. The clinical data of renal insufficiency differ from those usually observed with the ordinary type of nephritis in that there is no increase in blood-pressure, and little or no evidence of other circulatory disturbance. In practically every case the phenolsulphonephthalein output was markedly reduced, and in four instances the estimate was either zero or a faint trace. The stone was exceptionally large in the majority of instances, which explains the absence of acute pain, since large stones seldom obstruct urinary drainage.

In five other patients, although there was more or less clinical evidence of disturbance of renal function, the predominating symptom was that caused by marked secondary infection. Purulent urine was secreted by both kidneys, and the symptoms were marked by frequent attacks of chills and fever. In three of these cases there were multiple stones of variable size, and it was evident that their removal would be followed by considerable destruction of the kidney-tissue. It is this form of bilateral nephrolithiasis which offers the poorest prognosis following operation. One of the patients with multiple large stones was allowed to return home, and three years later was reported to be in fair health. Had she been operated on and the stone removed, it is a question whether she would have lived as long. In the other two patients the stones were small and evidently secondary to well-advanced pyelonephritis, the symptoms being due to renal insufficiency as well as to infection in one; the other was markedly benefited by pelvic lavage, but because of the absence of acute symptoms operation has been deferred.

Two patients had bilateral hydronephrosis complicated with stones; a point of unusual interest is that the stones were very evidently of secondary formation in a primary hydronephrosis. The stones were small and round and could scarcely be the etiologic factor of the urinary obstruction; they were evidently secondary deposits in the alkaline residual urine. Neither of these patients had secondary complications to warrant immediate operation, and when last heard from they were in fair health.

In two instances the stone was discovered accidentally. One patient complained of gastric symptoms only and was operated on for acute duodenal ulcer. The other had symptoms of marked circulatory disturbance and hypertension. Operation was not done in the case of one

patient, because the degree of cardiac insufficiency made it inadvisable. One patient was discovered to be pregnant at the time of examination, and operation was deferred until after pregnancy terminated. The patient had previously gone through an uncomplicated pregnancy without symptoms of nephrolithiasis, and it seemed advisable to allow the pregnancy to progress.

Two patients had been previously advised of stones in both kidneys, but they had not had symptoms of any kind in recent years. There was little or no evidence of infection in the urine and the renal function was but slightly impaired. Because of the previous history and evident tolerance of these patients it did not seem best to remove the stones. In the presence of large or multiple stones which are not causing acute pain, suppuration, or hemorrhage, the advisability of operation is questionable. The patient acquires a tolerance to the stones and will often have a better prognosis than if they are removed. If the stones are small and the function is not too greatly diminished, operation may be advisable in spite of the fact that there are no acute symptoms. If, however, there is considerable kidney-destruction, the removal of large stones causes so much damage to the kidney-tissue that death frequently results soon after operation. The possibility of stones recurring and then being situated so as to cause urinary obstruction, must also be considered.

Stone-forming kidneys.—A considerable group of patients with pain referred to both kidneys have been examined who gave a history of having passed stones repeatedly, but who at the time of the examination were found to be negative. Several of these patients had passed a stone within a week or so following thorough examination, including repeated roentgenography, cystoscopy, and pyelography. With a definite history of colic referred to the kidney, in spite of negative roentgenographic and cystoscopic data, a negative diagnosis of lithiasis should be made with caution. The inability of the x-ray to show this type of stone would lead us to believe that the occurrence of bilateral lithiasis is more frequent than can be ascertained by our present methods of diagnosis. The tendency to repeated stone-formation on the part of the kidney is most interesting. That it may be due to some disturbance in metabolism is suggested by the frequency with which the formation ceases after the diet has been corrected. Several of the patients with bilateral nephrolithiasis gave a history of having passed stones. In the presence of large or multiple stones it is probable that the stones passed sponta-

neously have been either single stones from a group or portions of single large stones.

Patients operated on.—Both kidneys were operated on in 33 patients and one only in 29 patients. Seven of the 29 patients were advised to have both kidneys operated on, but they refused. In the remaining cases either the stone was so small that it was believed that it would be passed spontaneously, or the condition of the patient did not permit of operation. Five of this group passed the stone from the other side spontaneously. The destruction of renal tissue consequent to the search and removal of very small stones is so great that it is usually best to await further developments, providing the patient can be kept under observation. When it is found advisable to remove such stones, pyelography has proved of great aid in their identification and localization.

Nephrectomy.—In 22 patients a nephrectomy of one kidney was found advisable because of the advanced destruction of the organ. In 7 of these patients a nephrectomy alone was made; in 15 it was found necessary to do either a pelviolithotomy or nephrolithotomy on the other kidney.

Postoperative results.—There was no operative mortality, which would indicate that patients with bilateral nephrolithiasis, when properly selected, offer no greater operative risk than with unilateral lithiasis. There were 10 deaths reported subsequent to operation, all within less than a year, the majority presenting clinical evidence of renal insufficiency.

Subsequent examination.—Twenty patients were examined at varying times following operation, and recurrences were found in 5. In correspondence with other patients, 3 gave a history of having passed stones from the kidney operated on, and 4 gave a history of severe pain, which we regarded as probably due to recurrence, thus making the total number of recurrences 12 (19.35 per cent). A previous review of patients with unilateral lithiasis showed a total recurrence of less than 10 per cent. It is evident, therefore, that the recurrence in bilateral nephrolithiasis is fully twice as great as with unilateral lithiasis.

In the 22 cases in which it was found necessary to do a nephrectomy because of calcareous pyonephrosis, 6 patients died within a year following operation. The prognosis, therefore, in cases of advanced calcareous pyonephrosis on one side is very grave. Subsequent examinations were made in 5 of these patients, recurrence being noted in but 1. Later,

letters were received from 3 patients, all of whom appear to be fairly well.

Unilateral Lithiasis with Disease in the Opposite Kidney

There were 15 cases of stone in one kidney and disease in the other. This group does not include a large number of cases in which an occasional pus-cell was found in the catheterized specimen from the opposite kidney. A few pus-cells are easily picked up by the ureteral catheter from the bladder-fluid, and should have no practical significance provided other cystoscopic data are negative and the function of the kidney is found to be normal. But with definite evidence of infection and disturbance in function in the other kidney, the question may arise whether or not operation would be advisable.

Among the various conditions found in the opposite kidney, pyelonephritis to a moderate degree was found in 6 cases, pyonephrosis to such an extent that the kidney was functionless in 5, hydronephrosis in 3, and tumor in 1.

Pyelonephritis in the opposite kidney.—In the presence of pyelonephritis in the other kidney it is advisable to ascertain as nearly as possible its functional activity. When the functional test is normal, the infection may disappear spontaneously following nephrectomy. When the function is moderately low, it is advisable to institute pelvic lavage and catheter drainage preliminary to operation. Uncomplicated pyelonephritis is usually painless. There was no pain referred to the kidney with pyelonephritis except in one instance, and the patient gave a subsequent history of having passed a small stone, with colic referred to the kidney where a pyelonephritis only had been previously diagnosed. When, therefore, a pyelonephritis on the opposite side is accompanied with pain, even though the roentgenographic evidence is negative, we must suspect the possibility of stone lodged in either the ureter or the kidney, and an exploration may be justifiable. Stone secondary to a chronic pyelonephritis is not a rare complication to renal infection, and was found in two of our patients. Removal of the stone, however, does not necessarily effect improvement in the pyelonephritis.

In two patients the nephritic element predominated and the infectious process seemed to be of secondary importance. The stone was removed from the cortex or end of the calyx, and it was hoped that its removal would improve the renal function. While both the patients

made a good temporary recovery, on subsequent correspondence and examination no definite change was noted in the condition.

One patient had a peculiar anomaly in that he had a reduplication of both ureters and pelves. The stone was situated in the upper pelvis of the left kidney, which was independent from the lower pelvis. The stone was removed by bisection of the kidney. Pyelonephritis remained in the lower pelvis and was also present in both pelves on the right side. The patient was recently examined (six years after operation) and was found in a fair degree of health, in spite of the persisting pyelonephritis, which seemed to be no farther advanced since the previous examination.

Inflammatory destruction of the kidney containing stone was so advanced that nephrectomy was necessary in three cases; the pyelonephritic kidney was left to carry on the function. Subsequent data from two of the patients lead us to believe that they are in a fair state of health. Whether or not the increased function in the remaining kidney had any therapeutic effect would be difficult to determine.

. *Pyonephrosis in opposite kidney.*—With pyonephrosis in the second kidney the indications for operation may be confusing: (1) When the function of both kidneys is greatly destroyed and there are no acute complications, the condition is not operable. (2) When there is even a small amount of normal tissue remaining in the calcareous kidney and there are acute symptoms which require relief, nephrolithotomy and drainage of the infected areas are indicated, the pyonephrosis in the opposite kidney being left undisturbed. (3) When the renal stone is not causing any acute disturbance and there is either pain or evidence of systemic infection from the opposite kidney, immediate nephrectomy of the latter is indicated. In this series there were a number in the first group, which have been previously referred to, there were 2 in the second group and 3 in the third group. The prognosis in the first two groups is necessarily very poor, all patients being reported dead within a few months after operation. In the third group there is generally a marked improvement in the condition of the patient. This is usually accompanied by improvement in the function of the remaining kidney, even though stone is present. In 1 patient the combined function rose from 19 per cent before operation to 40 per cent a month after operation. The predominating symptoms in 3 of the patients were on the side in which the stone was located, and in 2 patients on the side of the pyonephrosis. The discovery of stone in the latter was accidental.

Hydronephrosis in the opposite kidney.—There were 3 patients with hydronephrosis in the opposite kidney, and in 2 of these the hydronephrosis was bilateral, with secondary formation of stones. From the long duration of symptoms, extending back to childhood, it would seem as though the hydronephrosis were of congenital origin, although unilateral hydronephrosis of recent origin with secondary stones is not an uncommon condition. In 1 patient the stones had caused so much infection that the kidney was largely destroyed and a nephrectomy was necessary. The patient, however, died three months after leaving the Clinic. In another case a pelviolithotomy was done and the patient reports some improvement, with persistence of pain in both kidneys. The third patient was not operated on and reports the passage of numerous small stones and the cessation of symptoms a short time after leaving the Clinic. It is evident, therefore, that in the presence of complicating hydronephrosis a conservative operation is indicated when possible.

Tumor in opposite kidney.—In 1 patient a tumor was found involving the opposite kidney, which proved to be sarcoma. A nephrectomy was done, but was only partially successful, since there was infiltration in the surrounding tissues. No further operation seemed advisable.

Stone in a Single Kidney

In 7 patients with only one kidney a stone was removed. In 5 of these nephrectomy had been done elsewhere some time previously; in the other 2 there was no evidence of the existence of the opposite kidney, and there was no clinical evidence of previous renal disease, so it may be inferred that the condition was congenital solitary kidney. In 3 of the 5 cases in which a nephrectomy had been done this was necessary because of pyonephrosis—in 1 because of hydronephrosis and in 1 because of acute pyelonephritis. The operations performed on the single kidney were, nephrolithotomy 3, and pelviolithotomy 4. In one of the cases of nephrolithotomy the patient was operated on three times for recurring stone, extending over a period of six years. The patient died seven years after the first operation. One other patient was also operated on for repeated stone, but is now alive and well. This illustrates the great degree of tolerance which a single kidney may have for removal of recurring stone. One patient developed uremia one month after operation and died. One patient had a subsequent x-ray examination,

which was negative; there were no subsequent data in the remaining 3 cases.

A peculiarity noted in several of the cases was the high phenol-sulphonephthalein output of more than 50 per cent in spite of the presence of a stone of considerable size in the kidney. Had the opposite kidney been functionating, the output would have been considerably lowered by the presence of the stone, and the other kidney would have been performing a correspondingly larger amount of work. In the absence of the opposite kidney, however, the entire function was forced upon the one kidney, and the stone-irritation did not have the usual effect. There was no operative mortality in this group. Two of the patients have since been reported dead. The others are living and to all appearances are in comparatively good health.

Horseshoe or Fused Kidney

Five patients were operated on when lithiasis was found in a fused or horseshoe kidney—in 4 the lithiasis was confined to one-half of the kidney, and in 1 there was a stone in both sides of the kidney. In 2 patients with unilateral involvement secondary infection had advanced so far that bisection of the kidney was necessary. In 2 a pelviolithotomy was performed. In the case of bilateral nephrolithiasis, heminephrectomy was necessary on one side, and a stone was removed from the lower ureter by cystoscopic manipulation on the other. Three of these patients are alive from one to five years after operation.

Summary

1. In 17.2 per cent of the patients in this series there was bilateral renal involvement. The percentage of bilateral lithiasis was 12.3.

2. Bilateral as well as unilateral lithiasis occurred twice as often in the male as in the female.

3. Pain in bilateral nephrolithiasis was unilateral in 64 per cent and absent in 8 per cent of the cases.

4. Bilateral stones were found most frequently in the pelves and calyces.

5. Combined renal functional tests were of practical value only when normal or extremely low.

6. To ascertain the comparative degree of function in the two kidneys, the functional test was of value only when it was zero or a trace, normal or excessive.

7. The functional test, x-ray examination, and cystoscopic inspection may be insufficient to determine the degree of healthy renal tissue remaining, and exploration only can determine this.

8. Indications for operation: (*a*) The kidney with acute complications should be operated on first; (*b*) without acute complications the kidney with the better function should be operated on first; (*c*) occasionally simultaneous bilateral operation is advisable.

9. Patients may be inoperable because of renal insufficiency, secondary infection, kidney destruction, or constitutional complications.

10. Patients with large bilateral stones causing no symptoms or complications are better off without operation.

11. The operative mortality in this series was zero; the total number of deaths after operation, 10; these patients died less than a year following operation. The operative mortality with calcareous pyonephrosis is much greater than with other forms of bilateral lithiasis.

12. The recurrence in cases of bilateral nephrolithiasis was 20 per cent, in unilateral lithiasis, as previously reported, it was 10 per cent.

13. When there is stone in one kidney, the most common forms of disease in the opposite kidney are: Pyelonephritis, pyonephrosis, and hydronephrosis.

14. With unilateral lithiasis the opposite kidney may be so badly diseased that a preliminary operation may be advisable on that kidney.

15. Stone secondary to pyelonephritis, when removed, prevents further renal destruction, but is not of curative value.

16. When the nephritic element predominates, removal of the stone is not of much therapeutic value to the nephritis.

17. A single kidney has a great degree of tolerance for repeated operation for stone.

18. In a single kidney the phenolsulphonephthalein output usually remains high in spite of the presence of an uncomplicated stone which is probably due to compensatory hypertrophy.

19. Fused or horseshoe kidneys permit of repeated operation for lithiasis which may, if necessary, include heminephrectomy.

TUMORS OF THE URINARY BLADDER*

E. S. JUDD AND S. W. HARRINGTON

In the bladder, as elsewhere in the body, the correct surgery of tumors depends on discovering lesions early and removing them completely. The anatomic conditions of the bladder, and the rather inaccessible location of certain parts, together with the necessary maintenance of its physiologic functions, tend to make the technic of operation difficult.

Since the advent of the expert cystoscopist the clinical outlines of these neoplasms in the bladder have been definitely defined. If there is a tumor in any part of the bladder, it is not only demonstrable, but it is usually possible to show whether it is benign or malignant, and whether or not it is amenable to surgical treatment. The importance of removing a piece of the tumor through the cystoscope for microscopic examination has probably been overestimated. In most instances the appearance of the tumor reveals its nature. Further, it is generally believed that a large percentage of all tumors of the bladder are potentially malignant and should be treated as such. In papillary tumor, malignancy is suggested if there is necrosis of the papilla, edema at the base of the tumor, or nodules in the mucosa near the tumor. Intractable cystitis also suggests that the growth may be malignant, and any induration felt on rectal or vaginal examination is almost a certain indication that it is malignant.

It is also recognized that tumors having the characteristics of a benign papilloma may recur rapidly, and at the time of the recurrence present all the characteristics of a malignant lesion. Therefore it is difficult definitely to determine whether a papillary tumor of the bladder is benign or malignant, or what its clinical course will be. Fulguration is sometimes used to test the nature of the tumor; if benign, it usually responds quickly to intravesical treatment; if malignant, it may not

change—it may even be stimulated or the slough may not be separated, or it may become covered with a calcareous deposit, which suggests advanced malignant changes in the deeper tissues.

It is quite evident, from the recent reports by Geraghty, Braasch, Beer, Buerger, and others familiar with the cystoscopic picture in such cases, that they now depend more on the gross appearance of the tumor in determining its exact pathologic nature than formerly. When the endovesical removal of these tumors was simplified by Beer, it was thought that a method had been discovered that would be effective in curing all such cases. It gradually became apparent, however, that while certain types of tumors of the bladder could be readily removed by this method, other forms were little affected by it. It is now recognized that the endovesical method is applicable only to the treatment of tumors of the benign or relatively benign papillomatous type, and that non-papillomatous and definitely malignant papillomatous tumors should not be thus treated.

Several patients have come under our care who previously had been subjected to repeated fulgurations, apparently in spite of the fact that the tumor was growing rapidly instead of diminishing in size. One patient had received 20 treatments. These are unfortunate circumstances, since in all probability, if this patient had been operated on after the first few fulgurations failed to show improvement, much might have been accomplished. However, too much cannot be said in favor of this endovesical method of treating the type of tumors which respond to the treatment, yet it is very unfortunate to allow an operable case to become inoperable in the process.

The original cutting operations performed some years ago for tumors of the bladder were quite generally unsatisfactory, both from the standpoint of high mortality and early recurrence, but at the present time, with a better understanding of the nature of the lesion and with greatly improved operative technic, more radical and, therefore, more satisfactory operations can be performed. One of the principal difficulties in the open operation was the recurrence by implantation which so frequently followed and which was undoubtedly due to the piece-meal removal of the tumor through a small incision without adequate protection of the surrounding tissues. This particular feature has been almost completely eliminated, and I think occurs no more often now than in operations for malignant tumors in other regions. With the knowledge that these tumors readily form graft-recurrences it is neces-

sary to pay especial attention to the protection of other tissues during the time they are exposed.

From a therapeutic standpoint, tumors of the bladder may be classified as: (1) Those satisfactorily treated by endovesical methods, and (2) those requiring open operations. There is no question but that the benign papilloma will usually respond to fulguration. Exceptions to this would be the cases of multiple papillomas in which the treatments would be numerous and prolonged, or in cases in which the individual was not tolerant of this kind of treatment. It would be better to do an open operation in either instance.

It has been our custom to have all cases of tumor of the bladder examined cystoscopically at definite intervals following the original operation, with the view of keeping down any suggestion of a recurrence. In the past few years we have observed 14 cases of recurrence following resections which were amenable to fulguration. One of these patients was fulgurated fifteen months after the resection and has been well for two years. One was fulgurated after two years and has been well for four. One was fulgurated after eighteen months, and he now states that he is well, three years after the treatment. One was fulgurated after three years, and has not been seen for three months. One has been fulgurated yearly for the past three years, and was last examined five months ago.
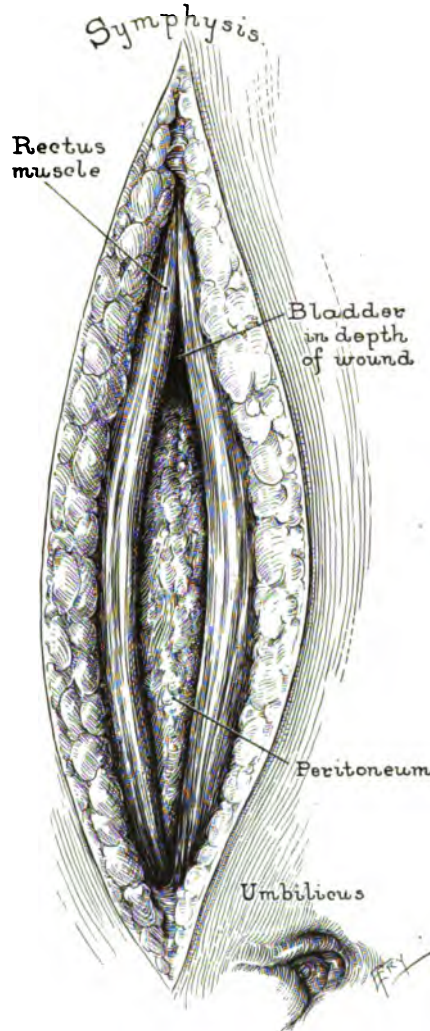
Fig. 63.—The incision extends from the umbilicus to the symphysis and down to the peritoneum.

One was fulgurated one month after operation and has not been seen for three months.

It seems evident that tumors, frankly malignant at operation, may respond to fulguration when they recur. In these cases in which a
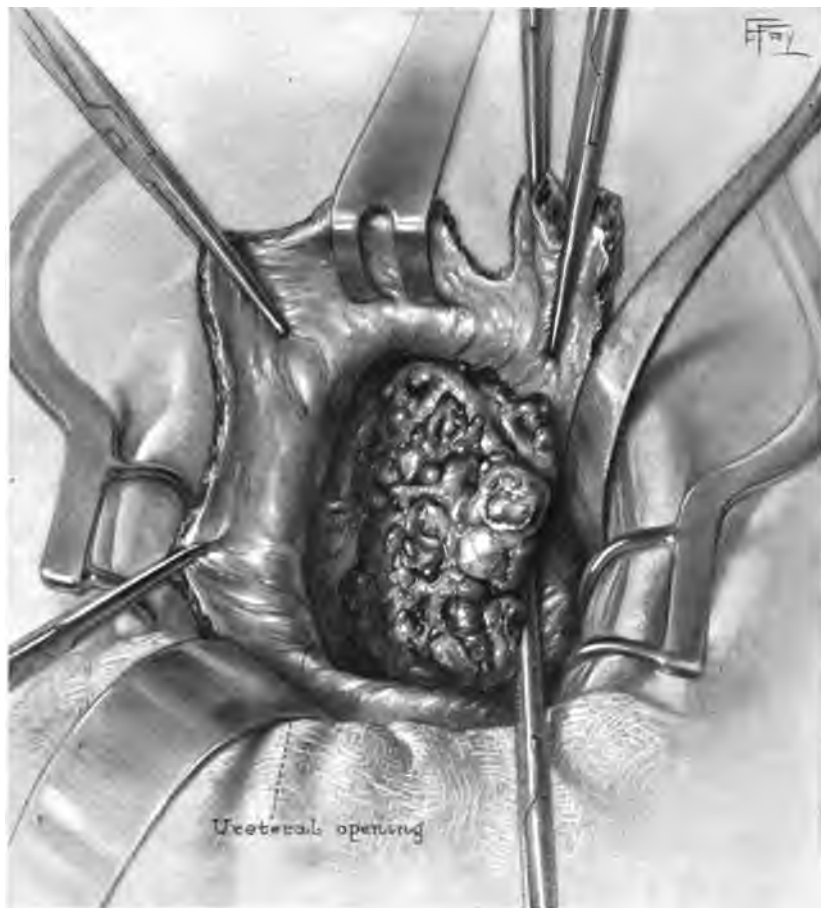
Fig. 64.—Large carcinoma involving the right base and lateral wall of the bladder.

resection has been done the granulating surface remaining after the tumor has been removed and the proliferating epithelium seen at the border of the granulating surface may often suggest a recurrence when none actually exists. It would seem best, however, in all such cases to keep close watch of conditions for some time and fulgurate any suspi-

cious-looking area before it has had time to develop into anything of importance.

In case the benign tumor does not respond readily to fulguration it should be removed by open operation. These papillomas, cystoscopically, simulate benign growths, and when they do not behave well under fulguration, it is suggestive that they may be malignant. All definitely malignant papillomas, either of the papillary type of carcinoma or of the type infiltrating the wall of the bladder, are best treated at once by the open operation. It may be permissible to treat a small malignant papilloma by fulguration with a view to radical excision, provided it does not respond readily. Undoubtedly the results in such cases at the present time would be much better if all malignant tumors of the bladder were treated by open operation as soon as they are discovered. After this, each case should be routinely cystoscoped every few months for one or two years.

All large benign tumors, such as myomas, fibromas, and angiomas, should be removed by suprapubic operation.

OPERATION

The operative procedure for tumor of the bladder consists in excising the tumor and resecting the portion of the wall of the bladder from which the tumor arises (Fig. 63). A simple excision of the tumor is permissible only in the case of a papillary tumor on a pedicle, and even with this form of tumor it is better to excise a portion of the adjoining bladder-tissue. Excision of the growth is not sufficient and is no safer than resection. In all cases the resection should include the entire thickness of the bladder (Fig. 64). Of course, this means the invasion of the prevesical space, but with modern technic this adds very little to the operative risk. If the resection is not extensive, the remaining opening may be closed, and drainage established through the bladder. If a large segment of bladder is removed, it is better to drain the space for several days (Fig. 65). The drain may be brought out through the bladder or along its side. If the prevesical tissues are exposed, drainage is essential (Fig. 66).

At one time we employed the transperitoneal method in a large percentage of our cases. At present it is not believed to be necessary or to have the distinct advantage formerly ascribed to it. If the peritoneal side of the bladder is involved, the peritoneum should always be opened and packed off to allow a complete removal of that part of the bladder,

'17—12

together with the peritoneum. This requires the performance of a more extensive operation, but apparently does not increase the mortality. If

Fig. 65.—Excision of growth shown in Fig. 64 completed. The extent of this growth made it necessary to remove nearly the entire right half of the bladder.

anything is to be gained in the exposure of, or in the thorough removal of, the neoplasms by opening the peritoneum, this should be done, although usually a fair-sized incision down to the prevesical tissues, without opening the peritoneum, is sufficient. In this manner all parts

of the bladder become accessible and a satisfactory resection can be

Fig. 66.—Completion of the operation. The bladder-edges are sutured together, obliterating the defect in the lateral wall. A large gauze drain is placed in the prevesical space and a rubber drain in the bladder.

made. The operation should be performed with the same precision as for the removal of malignant growths of the stomach or colon. Un-

fortunately, most tumors originate in the base of the bladder, and in a
large percentage of cases one of the ureteral areas will be involved.   The
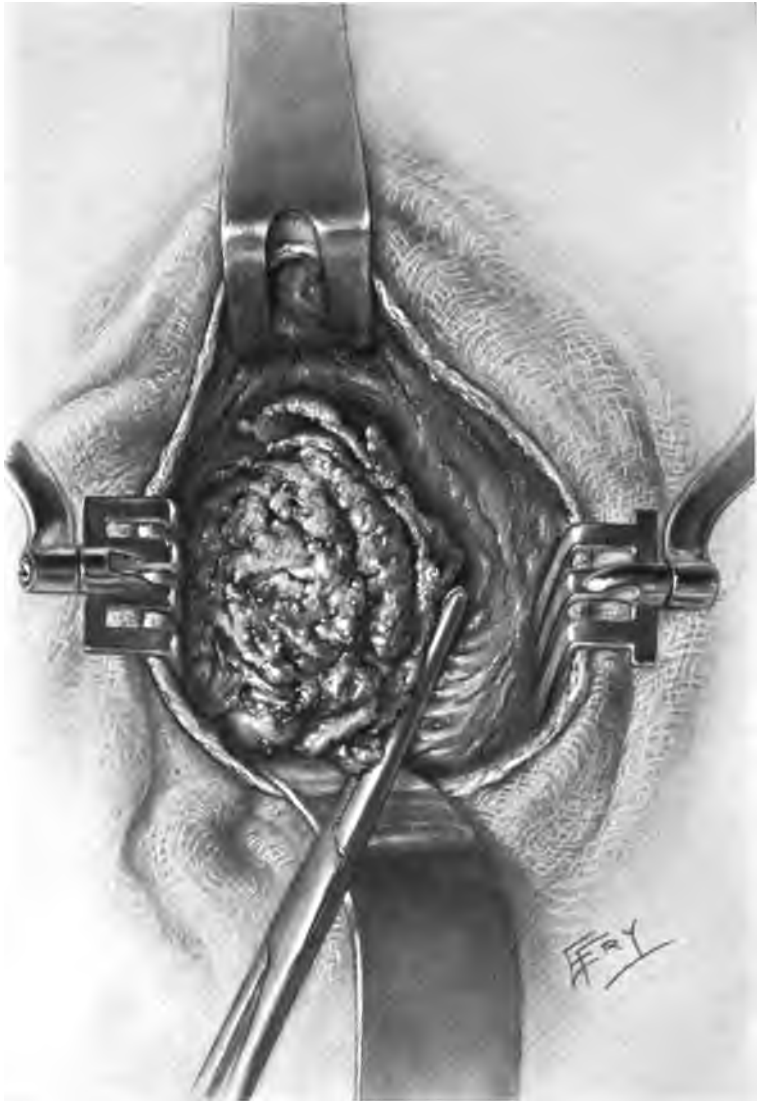
Fig. 67.—Papillary carcinoma with a large base extending over the right meatus.   The dissection is begun
outside the hemostat, the forceps grasping the healthy bladder-tissue.

most inoperable cases are those in which the urethral orifice is included
in the growth.   Such cases often require total cystectomy, a procedure
which as yet can seldom be advised.

Transplantation of one ureter to a new quadrant of the bladder may be done very satisfactorily (Fig. 67). In a few instances we have transplanted both ureters, but this will seldom be required, as the tumor,
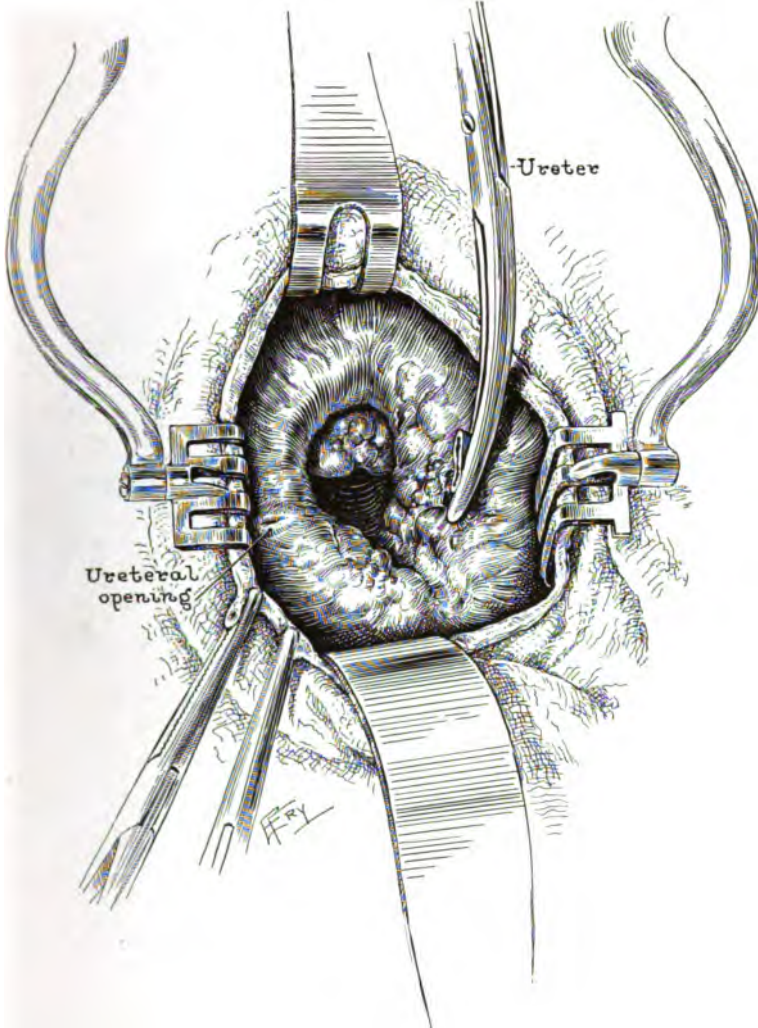
Fig. 68.—The same as Fig. 67, after the removal of the tumor. Half an inch of the right ureter has been removed with the growth. The hemostat is grasping the cut end of the ureter.

even when it is extensive, will usually involve only one side (Fig. 68). If the growth has completely occluded the ureter, the kidney on that side will probably be functionless, and in such cases, if it is difficult to make a satisfactory transplantation, it is just as well to ligate the ureter.

We have followed this procedure in at least 12 cases and have seen no harm of any description arising from it. In none of the cases was it necessary to remove the kidney later. If the divided ureter can be transplanted, it should be done.

Three cases are cited herein which have been followed for some time. In all, the kidneys were shown to be functionating normally; in one, four years; in one, one year; in one, six months after operation. In

Fig. 69.—Front view of intra- and extravesical papillary angiomyxoma.

these cases the urine from the transplanted ureter was practically normal. There were a few pus-cells in one case. The phenolsulphone-phthalein output from these kidneys was normal in two cases, and possibly reduced a little in the other. The case in which the ureter was transplanted four years previously gave a better output from the side operated on than it did from the opposite side. In 2 of the 3 cases ureteral catheters were passed into the transplanted ureters and

pyelograms were made showing normal outlines of the pelvis of the kidney. In the third case a goodly amount of urine was passing from the ureter, yet a catheter could not be inserted sufficiently to make a picture of the kidney. There can be no doubt that such cases are adequate

Fig. 70.—Sagittal view of intra- and extravesical papillary angiomyxoma.

proof that the kidney with a transplanted ureter continues to functionate in a normal manner. Infection does not take place in the kidney in spite of the fact that the ureterovesical sphincter is destroyed.

A large quadrant of the wall of the bladder may be removed and

good bladder-capacity be maintained. In some of our cases a mere funnel remained when the operation was completed, and yet in a short time the intervals between urination had diminished so greatly as to give the patient a very comfortable existence.

TABLE I

PATIENTS OPERATED ON FOR TUMORS OF THE BLADDER (1902–1916 IN-CLUSIVE AND FROM JANUARY 1 TO NOVEMBER 1, 1917), ALSO 80 PA-TIENTS TREATED BY FULGURATION SINCE JANUARY 1, 1911 (DR. BRAASCH)

Patients operated on (1902–1916)	181
Males	139
Females	42
Average age	54 years
Dead (average length of life, twenty months)	105
Alive	41
Condition unknown	35
Average duration of symptoms	26 months
Hematuria	154
Extraperitoneal operations	138
Transperitoneal operations	43
Extensive resections of the bladder	49
Intravesical transplantation of ureter	17
Ligation of the ureter	3
Cystectomy (complete extirpation of the bladder)	5
Both ureters transplanted to bowel	3
Both ureters transplanted to urethra	1
Both ureters brought out to the lumbar region	1
Growth excised with cautery or knife and cautery to the base	87
Inoperable cases—palliative cautery	26
Inoperable cases—explored	14
Pathologic diagnosis—epithelioma or carcinoma	180
Pathologic diagnosis—papillary angioma (included in this series)	1
Prostatectomy and operation on the bladder	3
Diverticulum excised and operation on the bladder	1
Stones removed and operation on the bladder	3
Patients reoperated on for recurrence	16
Patients having previous operations elsewhere	23
Tumors of the bladder	13
Prostatectomy	6
Removal of stones	4
Operations for malignant tumor (January 1 to November 1, 1917)	36
Extraperitoneal	29
Transperitoneal	7
Partial resection of the bladder	16
Extensive resection of the bladder	14
Ureter transplanted	8
Ureter ligated	6
Complete extirpation of the bladder (ureters transplanted to bowel)	1
Excision and cautery of multiple papillomas	3
Exploration of inoperable carcinoma	2

In conclusion it may be said that the treatment of tumors of the bladder is gradually being settled on a definite basis. A large experience with the endovesical treatment has demonstrated the type of tumor that may be cured by fulguration, and also the type that does not respond to this method of treatment. Further experience with the suprapubic open operation has taught us that a radical excision of the

tumor of the portion of the wall of the involved bladder and of the prevesical tissues may be done with satisfactory immediate and ultimate results.

ABSTRACT OF A CASE OF AN UNUSUAL TUMOR OF THE BLADDER (FIGS. 69 AND 70)

CASE 149248.—A female, nineteen years of age, came for consultation January 4, 1916. She complained chiefly of incontinence of urine, which began about two years previously, when there were partial loss of urinary control and slight pain at the end of urination. The bladder was irrigated for six weeks at that time, but with no improvement in the condition. The patient stated that there had been blood and pus in the urine for two weeks.

On physical examination a large cystic tumor was found in the midline, above the symphysis, and extending to the umbilicus. Catheterization seemed to reduce this mass to about three-fourths of the original size. Pelvic examination revealed a mass behind the bladder. Cystoscopic examination revealed a large tumor-mass involving the right wall and base of the bladder, and attached around the sphincter. The left meatus was normal; the right was not seen.

January 11, 1916: The first stage of the two-stage operation was done: Extraperitoneal removal of an enormous polypoid tumor, filling a greatly hypertrophied bladder. There was an opening in the right anterior wall of the bladder, through which the growth extended into the right extravesical space. This space was freed and packed off with the idea of removing the growth later.

February 19, 1916: The second stage was done: An extravesical growth, the size of a grape-fruit, was excised, and the opening in the bladder, two inches in diameter, was closed. The pathologic diagnosis was papillary angioma.

Although the patient had no symptoms, she returned for examination April 15, 1916. Cystoscopic examination showed a small, recurring papilloma on a pedicle at the right base, which was fulgurated. Cystoscopic examination October 28, 1916, and May 9, 1917, did not show recurrence in the bladder.

NOTES OF THE OPERATIONS AND OF THE EXAMINATIONS FOLLOWING OPERATION IN THREE CASES (80914, 186610, 163712) IN WHICH ONE URETER WAS TRANSPLANTED TO A NEW QUADRANT OF THE BLADDER AT THE TIME THE TUMOR WAS REMOVED

CASE 80914.—Mrs. J. R., forty years of age. Operation August 6, 1913: Suprapubic resection of the bladder for cancer was done. The lower end of the right ureter was involved; it was excised with the growth, the end of the ureter was cut off, and it was transplanted into the opening in the bladder. Cystoscopic examination was made October

26, 1917, four years after the operation, and showed the right ureter widely open. Clear urine was seen spurting from the meatus, but a catheter could not be passed into the ureter. A Garsan catheter was passed into the left ureter, blocking it completely. An intravenous phenolsulphonephthalein injection was given, and the output collected for fifteen minutes. Fifteen per cent came through the catheter in the left ureter, 17.5 per cent was collected in the bladder, this having come into the bladder through the right or transplanted ureter. The indications were that the right kidney was performing at least one-half of the renal function, in spite of the fact that the ureter had been transplanted four years previously. The urine was clean, but it was impossible to make a pyelogram of the kidney because a catheter could not be passed into the ureter.

CASE 186610.—P. K. O., a male, fifty-four years of age. Operation March 9, 1917: Suprapubic resection of the bladder for epithelioma. The resection involved the removal of one-third of the bladder, including one-half inch of the left ureter. The cut-off end of the ureter was transplanted into another part of the bladder. Cystoscopic examination seven months after the operation showed that the left ureter was widely open and spurting urine normally. A Garsan catheter was easily passed up into the ureter. Intravenous phenolsulphonephthalein appeared in four minutes: 4 per cent came from the transplanted side, and 20 per cent from the opposite side. A thorium pyelogram showed a normal outline of the pelvis of the kidney. There was no evidence of a recurrence of the carcinoma. This examination seemed to indicate that the function of the kidney was diminished, but in view of the fact that the ureter had been transplanted, it was difficult to get the catheter to fit snugly into it, and there was some leakage of urine from that side into the bladder, which undoubtedly helped to make up the 20 per cent.

CASE 163712.—H. P. J., a male sixty-nine years of age. Operation July 11, 1916: Suprapubic excision of a tumor of the bladder the size of a hen's egg, on the right wall. One-half inch of the lower end of the right ureter was removed with the growth, the cut-off end being pulled into the bladder and sutured so that it projected one-half inch. Cystoscopic examination more than one year after the operation showed an open right ureter and clear urine coming down from this side. The meatus was slightly gaping. A No. 6 catheter was passed readily up the right ureter. Fifteen per cent phenolsulphonephthalein was recovered from the right side, and 17.5 per cent from the bladder, showing that the right kidney was doing practically one-half the work. A pyelogram made of the right side showed a normal kidney-outline. There was no evidence of recurrence.

Forty-one patients are living, and their condition has been ascertained by letter or recent examination. The average age of these patients is fifty years. The average length of time since operation is fifty-four months, or four and one-half years.

TABLE 2

2	patients are	alive	10	years after operation		
3	"	"	"	9	" " "
3	"	"	"	8	" " "
2	"	"	"	7	" " "
2	"	"	"	6	" " "
3	"	"	"	5	" " "
5	"	"	"	4	" " "
5	"	"	"	3.5	" " "
1	patient is	"	3	" " "
6	patients are	"	2.5	" " "
4	"	"	"	2	" " "
5	"	"	"	1.5	" " "

Fifteen of the 41 patients have not returned for examination. In reply to recent letters they state that their general health is good. All but two have gained from 5 to 30 pounds in weight, and these two have maintained their normal weight. One complains of urinary frequency (five to seven times at night); the others void from one to three times at night. One only complains of frequency during the day. Three say that at times they have pain at the end of urination. None of the 15 patients have noted hematuria at any time since operation, nor has there been any subsequent treatment. The average length of time since operation in these cases is seventy-five months. In 7 an extra-peritoneal excision of the growth with the cautery was done; in 2 extra-peritoneal resections of the bladder with transplantation of one ureter; and in 6 transperitoneal excisions of the growth with the cautery.

In the 26 remaining cases the patients have returned for examination at various times since operation. The cystoscopic examination in 12 of these (three to eighty months after operation) showed no recurrence; and in recent letters they state that their general health is good and that they have no bladder symptoms. In the remaining 14 cases cystoscopic examination revealed recurrences which were later fulgurated or operated on.

ABSTRACTS OF THE HISTORIES OF THE 12 PATIENTS IN WHOM NO RECURRENCE COULD BE DEMONSTRATED FROM THREE TO EIGHTY MONTHS AFTER OPERATION

CASE 69825.—H. M., a male, aged fifty-four years. Operation July 6, 1912: Transperitoneal resection of the left one-third of the bladder with transplantation (intravesical) of left ureter. Cystoscopic examination was made eight months after the operation and showed no recurrence. In a letter received sixty-four months after the operation the patient stated that there were no symptoms. There had been no subsequent treatment.

CASE 86191.—Mrs. T. B., aged fifty years. Operation June 25, 1913: Resection of right one-half of the bladder with intravesical transplantation of the right ureter. A cystoscopic examination made forty-six

months after showed no recurrence. In a letter in fifty-three months the patient stated that there were no subsequent symptoms and there had been none.

CASE 80914.—Mrs. J. R., aged forty years. Operation April 13, 1913: Extraperitoneal excision with cautery for papilloma. A cystoscopic examination four months later revealed a recurrence. Operation August 6, 1913: Resection of right one-half of the bladder with intravesical transplantation of the right ureter. Cystoscopic examination forty-two months after the second operation showed no recurrence. In a letter forty-three months after operation it was stated that there were no symptoms.

CASE 104235.—J. A. W., a male, aged fifty years. Operation May 1, 1914: Extraperitoneal excision with cautery of one large papilloma from the left meatus and one small papilloma from above the urethra. Cystoscopic examination twelve months after the operation showed no recurrence. In a letter forty-two months after operation it was stated there were no symptoms.

CASE 110202.—I. U., a male, aged sixty-four years. Operation July 27, 1914: Excision with cautery of the left one-third of the bladderwall. Cystoscopic examination ten months later showed no recurrence. In a letter forty months after operation it was stated that there were no symptoms.

CASE 111047.—F. K., a male, aged forty years. Operation July 27, 1914: Excision with cautery of multiple papilloma of the bladder. Cystoscopic examination twenty-nine months later showed no recurrence. A letter was received forty months after operation, in which it was stated that there were no symptoms.

CASE 130930.—J. P. J., a male, aged forty-three years. Operation May 22, 1915: Excision with cautery of papillary carcinoma of the left wall of the bladder. Cystoscopic examination twenty-four months later showed no recurrence. In a letter received thirty months after operation it was stated that there were no symptoms.

CASE 129025.—Mrs. R. D. B., aged forty-four years. Operation April 23, 1915: Excision with cautery of a tumor two inches in diameter of the posterior wall of the bladder. Cystoscopic examination four months later showed no recurrence. In a letter thirty-one months after operation the patient stated that she had no symptoms.

CASE 142875.—Mrs. I. G., aged forty-six years. Operation August 16, 1915: Transperitoneal excision of a tumor of the left wall of the bladder. Cystoscopic examination in eight months showed no recurrence. In a letter twenty-seven months after operation it was stated that there were no symptoms.

CASE 164075.—Mrs. C. N., aged fifty-four years. Operation July 3,

1916: Extraperitoneal excision with the cautery of a carcinoma of the base of the bladder. A cystoscopic examination in three months showed no recurrence. In a letter received sixteen months later the patient stated that she had no symptoms except pain at times after voiding.

CASE 163712.—H. P. J., a male, aged sixty-nine years. Operation July 11, 1916: Extraperitoneal resection of one-third of the mucous membrane of the right wall of the bladder and transplantation of the right ureter (intravesical). A cystoscopic examination in fifteen months showed no recurrence. (Note page 186.)

CASE 113205.—R. N. A., a male, aged sixty-two years. Operation September 3, 1914: Extraperitoneal excision with cautery of a pedunculated papilloma of the bladder. Cystoscopic examination in eighteen months revealed no recurrence. In a letter thirty-eight months after operation he stated that he had no symptoms.

ABSTRACTS OF THE HISTORIES IN THE 14 CASES IN WHICH THERE WERE RECURRENCES AFTER OPERATIONS AND THE RECURRENCES WERE FULGURATED

CASE 68692.—H. G., a male, aged sixty-three years. Operation June 4, 1912: Transperitoneal excision with cautery of a growth at the trigone. Operation was done nineteen months later for a recurrence, at which time a transperitoneal excision of the growth was made with the cautery. Cystoscopic examination six months later showed no recurrence. Cystoscopic examination in eleven months showed a small recurrence which was fulgurated. The patient was cystoscoped again in twenty-six months, at which time a second recurrence was fulgurated. He was cystoscoped in sixty months, but no recurrence was found. In a letter in sixty-five months he stated that he had no symptoms.

CASE 95746.—J. W. H., a male, aged fifty-six years. Operation November 22, 1913: Extraperitoneal excision of one-third of the right wall of the bladder and of part of the urethra, with intravesical transplantation of the right ureter. Cystoscopic examination was made elsewhere every three months. No recurrence was found for thirty-one months, when three small papillomas were found and fulgurated. He has had repeated cystoscopic examinations since that time, but no recurrence has been found. In a letter forty-eight months later the patient stated that there were no symptoms.

CASE 235351.—M. T. R., a male, aged sixty-five years. Operation March 5, 1915: Extraperitoneal excision with cautery of a large papilloma. Operation again August 31, 1915: Extraperitoneal excision and cautery of two small papillomas of the left wall of the bladder (recurrence). Twelve months later fulguration of a suspicious area was done. In a letter in thirty-two months it was stated that the patient had no symptoms except some frequency at night.

Case 149248.—L. T., a female, aged nineteen years. (Note page 185.)

Case 102695.—Mrs. F. J. H., aged fifty-six years. Operation March 25, 1914: Extraperitoneal excision and extensive cauterization of a papillary carcinoma of the right bladder-wall. Cystoscopic examinations six months and twenty-six months after operation showed no recurrence. A recurrent growth was fulgurated thirty-nine months after the first operation. In a letter forty-four months later the patient stated that she had no symptoms.

Case 100111.—A. H. N., a male, aged fifty-three years. Operated on elsewhere six months before. Operation for recurrence February 7, 1914: Resection of the right one-third of the bladder and cautery applied. Operation November 5, 1914: Transperitoneal resection with cautery for recurrence. Cystoscopic examination six months and ten months later showed no recurrence. A cystoscopy was done in thirteen months, at which time a recurring growth was fulgurated. The patient was cystoscoped again in twenty-seven months, with subsequent fulguration for recurrence. He was again cystoscoped in thirty-nine months, when a suspicious area was fulgurated.

Case 119472.—J. H. H., a male, aged thirty years. Operation December 21, 1914: Extraperitoneal excision with cautery of multiple papillomas. The patient was cystoscoped five months later and a small recurrent growth was fulgurated. He was cystoscoped again in fourteen months, and a second recurrence found and fulguration done. In the nineteenth month radium was applied because of a third recurrence. Cystoscopic examination in twenty-two months showed no recurrence.

Case 77917.—W. J., a male, aged forty years. Operation January 6, 1913: Extraperitoneal excision and cautery of pedunculated papilloma. Cystoscopic examination in nine months showed no recurrence. Cystoscopic examinations were made fourteen, thirty-eight, and fifty-one months later, and recurring growths were fulgurated. In a letter in fifty-eight months it was stated that there were no symptoms.

Case 63897.—Mrs. H. O. S., aged thirty-one years. Operation February 14, 1912: Transperitoneal excision and cautery of multiple papillomas. Recurrence and operation August 19, 1913: Excision and cautery of one-third of the mucous membrane for multiple papillomas. Cystoscopic examination in thirty and forty-seven months revealed recurrences and fulguration was done. Cystoscopic examination in sixty-six months revealed no recurrence.

Case 58518.—O. H., a male, aged fifty-two years. Operation September 13, 1911: Resection with cautery of extensive papillomas involving left meatus, trigone, and dome. The patient was entirely well for sixty-two months, when there was frequency with blood-clots.

Cystoscopic examination revealed a recurrence at this time and fulguration was done. Cystoscopic examination sixty-five and seventy-two months after the first operation did not show recurrence.

CASE 106475.—H. K. A., a male, aged sixty-two years. Operation May 29, 1914: Extraperitoneal excision with cautery of papillary carcinoma of the right wall of the bladder. Cystoscopic examination in nineteen months showed a recurrence, and fulguration was done. Cystoscopic examination in forty months showed no recurrence, but a suspicious area which was fulgurated.

CASE 47732.—J. W. M., a male, aged forty-nine years. Operation January 10, 1911: Transperitoneal cautery-dissection of a papillomatous growth of the base and the right wall of the bladder. The prostate was removed at this time. The patient was cystoscoped elsewhere every three months, but no recurrence was found for sixty-three months, when three small growths were fulgurated. Cystoscopic examination in eighty months revealed no recurrence.

CASE 171792.—Mrs. J. A., aged fifty-seven years. Operation September 8, 1916: Transperitoneal resection of one-fourth of the left wall of the bladder. Operation August 19, 1917: Transperitoneal resection of one-third of the left wall of the bladder for recurrence and transplantation of the left ureter (intravesical). A cystoscopic examination was made in eleven months; a recurrence was found and fulgurated.

CASE 181230.—J. L. K., a male, aged fifty-six years. Operation December 31, 1916: Extraperitoneal excision and cautery for multiple papillomas of the bladder. Cystoscopic examination made in eleven months did not reveal recurrence.

REFERENCES

1. Beer, E.: The surgical therapy of benign and malignant tumors of the bladder. Jour. Am. Med. Assn., 1917, lxviii, 680–684.
2. Braasch, W. F.: Tumors of the bladder and their non-operative treatment. Minn. Med., 1918, i.
   Braasch, W. F.: Recent observations in cystoscopic technic. Ann. Surg., 1917, lxv, 615–620.
3. Buerger, L.: The pathological diagnosis of tumors of the bladder, with particular reference to papilloma and carcinoma. Surg., Gynec. and Obst., 1915, xxi, 179–198.
   Tumors of the bladder; their pathology and particular reference to the diagnosis of papilloma and carcinoma. New York Med. Jour., 1917, civ, 841–843.
4. Geraghty, J. T.: Fulguration in treatment of bladder tumors. Surg., Gynec. and Obst., 1915, xxi, 150–154.
   The result of treatment of bladder tumors. Jour. Am. Med. Assn., 1917, lxix, 1336–1342.
   Treatment of bladder tumors. New York Med. Jour., 1916, civ, 838–840.

EXSTROPHY OF THE BLADDER AND ITS TREATMENT*

C. H. MAYO

Exstrophy of the bladder is a rare congenital malformation; it is reported by Neudörfer as occurring once in 50,000 births. The anomaly is probably occasioned by variations of the salts in the amniotic fluid surrounding the embryo. It is one of the most serious malformations, as approximately one-half of those suffering from it die during the first ten years of life, and the great majority are dead before they are forty. The condition is very distressing, from the tenderness and the difficulty of protecting the protruding bladder, the constantly dribbling urine requiring much absorptive dressing or an equally foul-smelling receptacle, which leads such persons to shun society. Associated defects are epispadias in the male, an absence of the anterior pubic bone in all cases, and an apparent absence of the umbilicus, which becomes the upper margin of the mucocutaneous juncture, the urachus being absent. In the case of a child of five in whom exstrophy was the result of assault it was asserted that the pubic bone later disappeared causing the condition to resemble congenital exstrophy.[16] The lack of the pubic arch makes the pelvis apparently wider, and the sacro-iliac joints become fixed early. In the female procreation is possible. Winslow has reported the condition in a woman who had given birth to four children (Fig. 71).

The various measures for improving the condition are plastic skin covering or closure of the bladder mucosa. This method was highly developed by Roux in 1852, and has been variously modified since by Thiersch, Nélaton, Wood, and others. The great defect by the plastic closure methods came from the necessity of using hair-growing skin, which later accumulates lime deposit and adds to the foulness of the uncontrolled bladder. Passavant aided the closure by compressing the

half-formed pubic arches, and Koch, König, and others made sub-
cutaneous section of the bony arches.   Trendelenburg added to this
method the partial separation of the sacro-iliac joint to more nearly
approximate the pubic arches over the bladder.   The septic uncon-
trolled pouches formed by these operations made it possible to wear
some sort of drainage apparatus in which a portion of the urine could
be accumulated, but the danger of diseased kidneys from ascending
infection was actually increased.   Additional methods of treatment
were devised by Subbotin and Lerda, who, before closing the bladder,
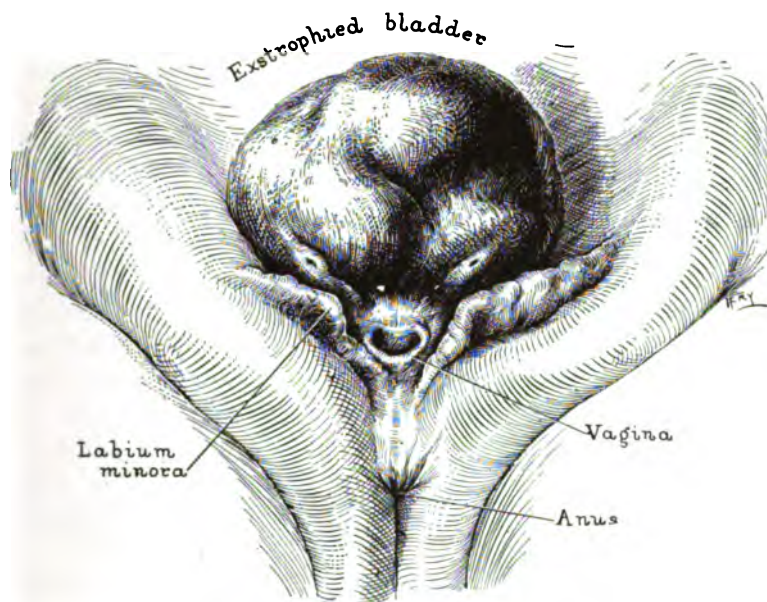
Fig. 71.—Exstrophy of bladder in the female; exposed mucosa with ureteral openings.

tunneled a space between the sphincter ani and the rectal mucosa and
drew through it a folded strip of bladder-wall as a tube, the anal sphinc-
ter closing the new urethra as well as the anus.   The operative mortality
in these cases was 25 per cent, and the bladder still remained a septic sac.
    Another method for the relief of the deformity was to construct
other closed cavities to serve as a bladder.   Gersuny separated a loop
of bowel and after establishing the continuity of the alimentary canal,
brought the lower end of the loop through a tunnel opening within the
anal sphincter, as in the Subbotin method, the ureters being inserted
into the upper end of the loop, which also developed a septic tank.   The

'17—13

operation of Makkas developed a bladder from the cecum. The ileum was divided at the ileocecal valve, which was closed on the cecal side, the ascending colon divided and both ends closed, and the ileum joined end-to-side in the upper segment of the ascending colon. The appendix was brought through the abdominal wall as an appendicostomy, the new bladder being emptied at regular intervals by a catheter passed through the appendix. This operation was performed in 1910. I saw his patient two years afterward. At that time the ureters were enormously dilated from the cecum to the kidneys, and the new bladder was septic. The cloaca of birds was looked on as a solution of the problem. The ureters were joined to the sigmoid or rectosigmoid and the rectum was utilized as both a fecal and urinary receptacle. The high mortality of this method showed a necessity for improvement in technic, but the control was good. To avoid ascending infection and dilatation of the ureters the sigmoid was divided, the proximal sigmoid joined end-to-side into the rectosigmoid, and the ureters inserted into the upper end of the distal sigmoid. While the feces did not flow over the ends of the ureters directly, the gas, fluids, and bacteria could not be prevented from causing infection and there was but little improvement in the mortality. Other methods were to insert the right ureter into the appendix and the left into the sigmoid, but with these also there was ascending infection of the kidneys.

The next modification was to preserve the small openings of the ureters as they passed through the walls of the bladder, in the belief that this mechanism was nature's safeguard against infection. The Maydl operation, developed in 1892, removed the base of the bladder with the ureters attached and inserted the reversed segment into an incision in the anterior wall of the rectum. The operation is performed extraperitoneally and has been done transperitoneally. In the male it is not difficult, but in the female it is complicated. By this method Russian surgeons report a mortality of 32 per cent, Orlow a mortality of 17 per cent in 61 cases, and Drucbert a mortality of 27 per cent in 81 cases, within fifteen days of the operation. We operated on 3 patients by this method and 2 died. Moynihan uses a larger area of the bladder in the Maydl operation, thus greatly increasing the rectal capacity. Sherman's work with Peter's modification, based on the belief that the protection is in the small orifice of the ureter, was to dissect the ureter out of the bladder, retaining the mucus-covered ends intact, and to transplant them into the rectum.

It is true that nature's method of emptying a duct is always by indirection; thus the salivary ducts, the common duct of the liver, and the ureters pass through the muscularis and continue for a distance between the mucous membrane and the firmer outer wall of the cavity. Pressure from within compresses the ducts and blocks against dilatation and ascending infection. The fact seemingly was not recognized that the mechanical principle of the passage of the ureter through the wall of the bladder and its mucosa could not be retained after the loss of its innervation. The surgical principle of such duct entrances is recognized in the Witzel operation of gastrostomy and enterostomy, in which leakage is prevented by the tunnel made by folding the wall of the stomach or bowel over the tube for $1\frac{1}{4}$ inches. The Stamm-Kader method accomplishes the same thing by a series of purse-strings, a funnel entrance being made into the viscus.

The secret of successfully anastomosing the ureter into the bowel is to tubularize the ureteral entrance for $1\frac{1}{4}$ inches. There are two methods of doing this. Stiles followed the plan of the Russian and Polish surgeons of passing the ureter into the intestine through a small opening, and depressing it into the bowel, which is folded over it, the folds being held by suture; the mechanism then consists of the ureter surrounded by the whole thickness of the wall of the intestine—the Witzel method. Coffey's modification was first developed for the treatment of obstruction of the common duct of the liver by uniting it with the duodenum, and has proved most efficient for ureteral transplantation. It does not narrow the lumen of the intestine, and is carried out as follows: The peritoneum and muscularis are incised longitudinally for $1\frac{1}{4}$ to $1\frac{1}{2}$ inches, down to the mucous membrane, but not through it. The incision is best made in the firmer longitudinal bands of the wall of the sigmoid. The ureter is exposed by an incision in the peritoneum in the posterior pelvic wall, and is isolated to within 1 or $1\frac{1}{2}$ inches of the bladder, where it is divided and the distal end ligated. From $2\frac{1}{2}$ to 3 inches of the ureter are separated, the posterior peritoneal incision is closed by suture to the point where it emerges, the lower end of the ureter is split for $\frac{1}{4}$ inch, a curved needle with chromic catgut is passed through the end, the catgut tied, and the short end of the thread cut.

The mucous membrane in the lower end of the incision in the wall of the intestine is now perforated into its lumen. In preparing for this, and to prevent contamination of the wound, a large, curved, rubber-covered

clamp is used to hold the bowel in position, and the union is made within the curve of the clamp. The curved needle on the catgut attached to the end of the ureter is passed into the lumen of the bowel through the small opening, and out of the wall of the bowel ½ inch below it. Drawing the chromic catgut suture pulls the end of the ureter into the lumen of the bowel. The needle is then passed once through the peritoneum and muscularis in order that the catgut may be tied to hold the ureter fixed within the wall of the intestine. The sides of the incision in the outer wall of the bowel are closed over the ureter, the needle including its outer tissue in two or three sutures. A second row of peritoneal
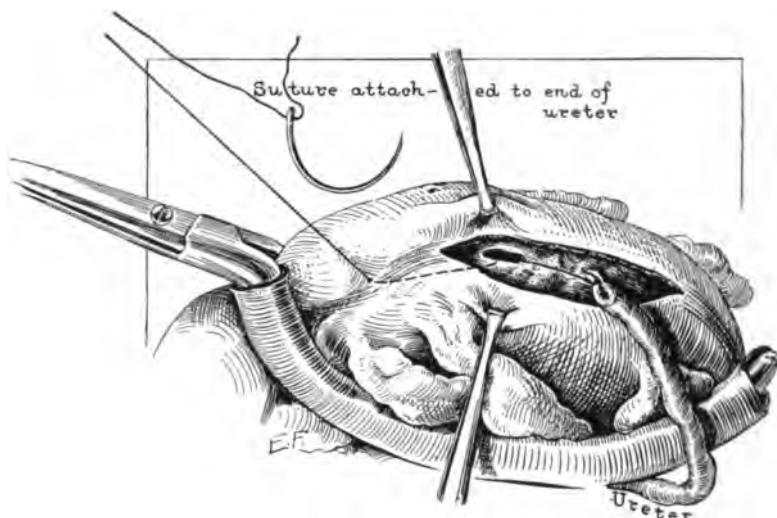
Fig. 72.—Ureter ready to be drawn through incision, into lumen of bowel.

sutures is placed over this, extending down over the tied knot of the fixation suture, which holds the ureter in place (Figs. 72 and 73). This gives the ureter a natural duct entrance. The slightest pressure from within closes the duct, but not sufficiently to prevent the delivery of urine by the automatic and intermittent waves of contraction occurring about six to eight times a minute during the period of activity.

The abdominal incision for the work is a low lateral pelvic incision, and is best made on the right side first. As the sigmoid naturally passes to the left it can always be reached, while if the incision is made on the left side first, the slack bowel may have entirely disappeared from the attachments of the former operations. The intestine is held by a few

sutures to the posterior peritoneum, so as to cover the ureteral entrance. It is best to do but one side at the first operation, as the urine is absorbed from the large bowel, as in a Murphy drip. Tolerance is soon acquired, however, and the slight uremic mental apathy disappears in a week. The second ureter may be transplanted with no trouble in from one to two weeks after the first operation. A small tube may be kept in the rectum for the first few days unless it adds to the discomfort. Usually at once or at least within a few days the urine will be passed at moderately frequent intervals.

The right half of the colon is the absorbing side of the intes-
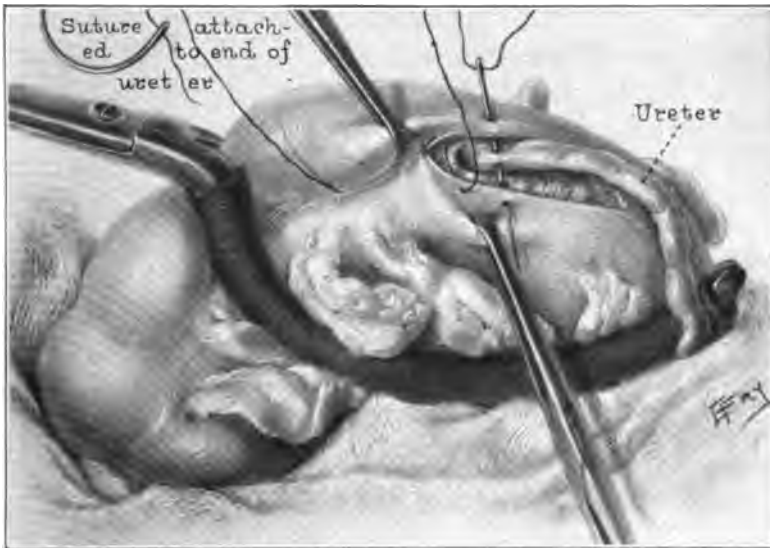
Fig 73.—Infolded ureter in large bowel similar to gastrostomy.

tine. Little work is done by the lymphatics, nearly all absorption being by osmosis, and the fluids are taken by the portal circulation to the liver. It is not good judgment to use the right side of the colon for an anastomosis. Experimental work recently reported,[1] in which it was hoped that, by utilizing a natural duct entrance into the intestine, ascending infection could be avoided, showed that one ureter could be passed through the duct of Santorini and the absorption of the urine from one kidney would not give marked symptoms, though when the second ureter was inserted, the animals died from uremia. This was also shown in Connell's experiments, in which the small intestine

was used. Therefore we must keep to the large bowel, and preferably to its lower end. Transplanting the ureters is advisable in the few cases in which extensive destruction of the base of the bladder and urethra have occurred following childbirth.

Children should be old enough to be able to attend to their own needs; that is, from three and one-half to five years of age. In early life, also, there may be defects in the innervation of the rectum, and if prolapse of the rectum accompanies the exstrophy, this condition must be overcome by time or by operation before the cloacal condition is instituted. After the age of forty it is probable that ureteral anastomosis with the skin in the back is best from the standpoint of low mortality and future length of life. In this position receptacles can be readily adjusted for the collection of urine. The report of the cases mentioned below reveals the important fact that after operation these children were able to go to school and receive an education, which was impossible in their former state. The older ones are all working. One young woman has taken a three-year course in nurse's training, and a year ago passed through an attack of erysipelas without bad results.

Since 1896 we have seen 37 patients with exstrophy of the bladder. Fifteen of these were not operated on at the time of their examination, some were too young to be operated on, and the others expected to return for operation. Six patients were operated on by the plastic method. One died six months later (traumatic exstrophy at childbirth; the child weighed 12.5 pounds). The plastic operations did not afford control of the urine. Three patients were operated on by the Maydl-Moynihan method, and two died in the hospital of uremia. Thirteen were successfully operated on by the transplantation method, with one operative death. One died from pneumonia a few weeks after leaving the Clinic. One died three years after operation from pulmonary tuberculosis, and one three years after operation from typhoid fever.

REFERENCES

1. Baird, J. S., Scott, R. L., and Spencer, R. D.: Studies on the transplantation of the ureters into the intestines. Surg., Gynec. and Obst., 1917, xxiv, 482–484.
2. Coffey, R. C.: Physiologic implantation of the severed ureter or common bile duct into the intestine. Jour. Am. Med. Assn., 1911, lvi, 397–403.
3. Connell, F. G.: Exstrophy of the bladder. Jour. Am. Med. Assn., 1901, xxxvi, 637–668.
4. Drucbert, J.: Les résultats eloignés de l'opération de Maydl dans l'exstrophie vésicale. Écho méd. du nord, 1904, 481–484.
5. Gersuny: Wien. klin. Wchnschr., 1898, No. 43. Quoted by Connell (Note 3).
6. Kader, B.: Zur Technik der Gastrostomie. Zentralbl. f. Chir., 1896, xxiii, 665–670.

7. Koch, C. F. A.: Eine modificirte Trendelenburg'sche Blasenspaltenoperation. Zentralbl. f. Chir., 1897, xxxvi, 953–956.
8. König: Verhandl. d. deutsch. Gesellsch. f. Chir., 1896, i, 77.
9. Lerda, G.: Contribution au traitement de l'exstrophie de la vessie. Jour. de chir., 1913, x, 549–562.
10. Makkas, M.: Zur Behandlung der Blasenektopie. Umwandlung des ausgeschalteten Coecum zur Blase und der Appendix zur Urethra. Zentralbl. f. Chir., 1910, xxxvii, 1073–1076.
11. Maydl, K.: Über die Radikaltherapie der Blasenektopie. Wien. med. Wchnschr., 1894, xliv, 25–29; 1896, xlvi, 28–31.
12. Moynihan, B. G. A.: Extroversion of the bladder: Relief by transplantation of the bladder into the rectum. Ann. Surg., 1906, xliii, 237–240.
13. Nélaton: Gaz. hebd. de méd., 1854, i.
14. Neudörfer: Quoted by Boogher, J.: Exstrophy of the bladder. Urol. and Cutan. Rev., 1916, xx, 376–377.
15. Orlow, L.: Traitement opératoire de l'exstrophie de la vessie; transplantation des urétères par le procéde de Maydl. Rev. de gynéc. et chir. abd., 1903, vii, 795, 852.
16. Packard, H.: Eversion of bladder as a late sequel of multilation caused by rape in early childhood. Ann. Surg., 1914, lix, 555–557.
17. Passavant, C.: Die Blasen-Harnröhrennaht mit Vereinigung der Schambeinspalte bei angeborener Blasenspalte mit Epispadie. Arch. f. klin. Chir., 1887, xxxiv, 463–500; 1890, xl, 1.
18. Roux, J.: Exstrophie de la vessie. Union méd., 1853, vii, 449, 453.
19. Sherman, H. M.: Exstrophy of the bladder successfully treated by Peter's method. Jour. Am. Med. Assn., 1905, xlv, 890–892.
20. Stamm, M.: Gastrostomy; a new method. Tr. Ohio Med. Soc., 1894, xlix, 164–168; Med. News, 1894, lxv, 324–326. Kader, B.: Zur Technic der Gastrostomie, Zentralbl. f. Chir., 1896, xxiii, 665–670.
21. Stiles, H. J.: Epispadias in the female and its surgical treatment. Surg., Gynec. and Obst., 1911, xiii, 127–140.
22. Subbotin, M.: Neues Verfahren zur Bildung der Harnblase und Harnröhre mit einem Sphincter aus dem Mastdarm bei Exstrophia vesicæ, Epispadie hohen Grades und Urininkontinenz. Zentralbl. f. Chir., 1901, xxviii, 1257–1260.
23. Thiersch: Verhandl. d. deutsch. Gesellsch. f. Chir., 1882, xi, 89. Also: Zentralbl. f. Chir., 1876, 504. Quoted by Connell (Note 3).
24. Trendelenburg, F.: Zur Operation der Ectopia Vesicæ. Zentralbl. f. Chir., 1885, 857–886: Ann. d. mal. d. org. gén.-urin., 1903, 782.
25. Winslow, R.: Report of a case of exstrophy of the bladder operated on nearly thirty years ago, with subsequent history. Surg., Gynec. and Obst., 1916, xxii, 350–352.
26. Witzel, O.: Zur Technik der Magenfistelanlegung. Zentralbl. f. Chir., 1891, xviii, 601–604.
27. Wood, J.: Exstrophy of the bladder. Brit. Med. Jour., 1880, i, 278.

STUDIES IN THE TRANSPLANTATION OF WHOLE ORGANS

I. AUTOTRANSPLANT OF THE LEFT KIDNEY TO THE NECK, WITH RIGHT NEPHRECTOMY, IN THE DOG*

C. DEDERER

The following experiments were undertaken to perfect the technic of organ transplantation with reëstablishment of circulation and function. The neck was chosen for the site of the transplant, because here the excretion can be readily observed and collected.

The first experiments in transplanting the kidney to the neck were done by Ullman, who in 1902 performed the operation in a dog. It was later tried by Carrel, Carrel and Guthrie, Floresco, and Borst and Enderlen. Of these experiments, the most successful was that by Floresco, who obtained a functioning transplant which excreted bloody urine for eight days. The kidney was removed on the ninth day because of necrosis. Floresco contributed much to the subject by discovering the destructive effect of perfusing transplants with saline solutions. Guthrie has also laid great stress upon this point. In 1910 Villard and Tavernier attempted the operation with more success. They obtained a functioning transplant which remained in the neck for sixty-eight days, but without removal of the other kidney.

TECHNIC

Abdominal and cervical incisions are made simultaneously. The assistant exposes the kidney, while the cervical vessels are being cleaned of their outer fibrous coats. The renal artery and vein and the ureter are freed, cleared, and sectioned. The vessels are emptied of blood and washed with liquid petrolatum from a bulb syringe. The vessels are sutured with prepared raw silk threaded on No. 16 needles, Murphy

plain "over and over" stitch with Carrel stay-sutures and dark background being used. The ureter is led through a small separate wound in the skin. The wounds are sutured with linen. Collodion-gauze dressing is used. The ureter is covered with a wet dressing of neutral solution of chlorinated soda. Fig. 74 shows some of the details of the technic.

In these experiments there were five partial successes before complete success was obtained:

<p align="center">TABLE 1.—DETAILS OF EXPERIMENT</p>

DATE OF OPERATION	DOG No.	EXPERIMENT No.	TIME OF OPERATION	CIRCULATION CUT OFF	FUNCTION	REMARKS
3/16/17	B870	243	3 hours 20 minutes	Not recorded	None	Operation too long. (Dog recovered.)
3/30/17	B919	311	2 hours 26 minutes	44 minutes	None	Distemper, pneumonia.
4/ 6/17	B936	332	2 hours 41 minutes	54 minutes	None	Peritonitis from tearing apart transverse wound.
4/13/17	B949	345	2 hours 21 minutes	57 minutes	6 days	Pyelitis of the transplant; foreign body in the rectum; distemper; pneumonia.
4/20/17	B960	356	2 hours 15 minutes	48 minutes	2 days	Renal vein anastomosed to the inferior thyroid vein. Distemper; pneumonia.
5/ 2/17	B976	388	1 hour 41 minutes	32 minutes	4 mos. 1 day	Successful. For details see Protocol.

<p align="center">COMMENT</p>

The fourth experiment furnished some interesting data. Twelve days after the transplantation a catheter was placed in the bladder and a ureteral catheter in the ureter of the transplanted kidney. One cubic centimeter of phenolsulphonephthalein was injected into one saphenous vein. In four minutes the phenolsulphonephthalein appeared in the urine from the transplanted kidney. In the first hour 17 c.c. of urine were collected from the transplanted kidney and 17 c.c. from the bladder. The specimen from the transplant contained 1.44 per cent of the phenolsulphonephthalein. In the second hour the transplanted kidney excreted 13.5 c.c. of urine with a trace of phenolsulphonephthalein, while only 12 c.c. were obtained from the bladder, The urine from the bladder showed no phenolsulphonephthalein during the first two hours. On one occasion the end of the ureter was seen to move during contraction. Specimens from this dog are shown in Figs. 75, 76, and 77.

Figure 76 shows the second cervical nerve after it had been dissected away from the new perirenal tissues, in which it spread out in all directions.

Fig. 74.—Anastomosis of the left renal artery to the right common carotid artery, and the left renal vein to the right external jugular vein. Natural size.

PROTOCOL OF SUCCESSFUL EXPERIMENT

EXPERIMENT 388 (Dog B976).—An adult, female, mongrel fox-terrier, weighing 8.6 kilos, with short hair, was operated on May 2, 1917.

8.58 A. M.: Intratracheal ether anesthesia was begun.

9.15 A. M.: Incision was made.

9.40 A. M.: Vessels of the neck were clamped off with Crile clamps.

9.48 A. M.: Renal vessels were clamped.

10.20 A. M.: Circulation was reëstablished through the kidney.

10.56 A. M.: Last stitch was taken in the wound.

11.05 A. M.: Anesthesia was stopped.

TABLE 2.—AUTOTRANSPLANTATION OF KIDNEY (PROTOCOL, Dog B976)

DATE 1917	GENERAL CONDITION	NOTES ON WOUND	FLOW OF URINE FROM NECK	EXAMINATION OF URINE		TREATMENT*
				Gross or chemical	Microscopic	
5/2	Wt. 8.6 kg. Excellent.	Operation.	Flow in spurts.	Phthalein appeared in 7 minutes.	...	Dakin dressing.
5/3	Excellent.	Collodion gauze loose.	Waves of urine.			Dakin dressing.
5/4	Eye and nasal discharge.	Serum let out.	7 waves to minute.	Amber, clear; alkaline. faint trace albumen.	Few leukocytes, erythrocytes and epithelial cells.	Boric acid nose and eyes.
5/5	Excellent.	Neck excoriated with urine.	Waves of urine.	Amber, clear, alkaline.	Many leukocytes, ammonium urate crystals.	Boric acid nose and eyes.
5/7	Excellent.	Slight discharge.	2-6 waves per min.	...	Scattered leukocytes.	Metal collar, no dressing.
5/8		No discharge.	Waves every few seconds.	...	Few leukocytes.	Silver nitrate to wound.
5/9	Very lively.	...	7.5 c.c. in one hr.†	Alkaline; 0.24 per cent urea and ammonia.		Dram sodium bicarbonate.
5/15	Wt. 8.9 kg.					½ dr. sodium bicarbonate.
5/16	Wt. 8.7 kg.	Right nephrectomy.	60 c.c. per hour.†	Light amber.	...	½ dr. sodium bicarbonate; zinc ointment.
5/17	See Fig. 78. Watery nasal discharge.	Slight discharge from neck.	45 c.c. per hour.†		...	
5/18	Active, interested.	New collar necessary.	Squirted a foot once.	Light amber; alkaline; no albumen; 0.3+ per cent urea.	2 or 3 clusters leukocytes. No epithelial cells.	Petrolatum with chlorinated lime; licked off.
5/19	Active, runs; became drowsy, dizzy.	Lumbar collodion gauze; partly chewed off.	Licked urine and chlorinated lime from legs.	Very light amber.		Dram sodium bicarbonate.
5/20	Good.	Loin incised because of swelling.	Free flow.			Cold; brought in shivering.
5/21	Very active.	Dakin dressing on loin.	Dripping.			Dram sodium bicarbonate. Dakin dressing.
5/22	Excellent.	Dakin dressing on loin.	Squirted over 12 inches.			Shown at County Medical Society.
5/23	Excellent.	Dakin dressing on loin.				
5/24	...	Dakin dressing on loin.	Squirted from neck; head stationary.			Dakin dressing. Ate aluminum and rubber collar. Zinc ointment.
5/25	Excellent.	Neck abrasions from lack of collar and rubbing neck.	...			
5/26	Excellent.	Bit off leather collar.				Sodium bicarbonate.
5/27		Pus from punctured loin abscess.	...			Leather-metal collar bitten off.
5/28	Excellent.	Pus from punctured loin abscess.				...
5/29	Excellent.	Abscess closed over.	No injury to ureter from lack of abscess. 4 c.c. in 8 min., or 30 c.c. per hour.	0.63 per cent urea—and ammonia.	...	...
5/30	Wt. 8.1 kg. Good.	Abscess opened again.	...		...	Original collar on.
5/31	Wt. 8 kg. Good.	Loin wound drains through small hole.	...			0.2 gm. calcium chlorid.
6/1	Wt. 8.3 kg. Good.		...			Belt collar on again.
6/2	Wt. 8 kg. Excellent.	...	...		...	Zinc to neck.
6/3	Wt. 8 kg. Excellent.	...	...			Boric acid nose and eyes (dusted).
6/4	Wt. 8.5 kg. Excellent; cough.					
6/6	Wt. 7.8 kg. Fine spirits.	...	...		...	Collar left off.
6/7	Wt. 8.9 kg. Excellent.	Slight discharge	...			
6/27	Excellent.					
6/29	See Fig. 79.	Loin wound moist.	Spurts 1 meter away.	Amber, clear, alkaline.	No cells or detritus.	Photograph taken.
8/18						

* Amount of sodium bicarbonate only estimated. It was taken with food and some lost.   † Urine collected by catching drops. Very small error makes estimation necessary.
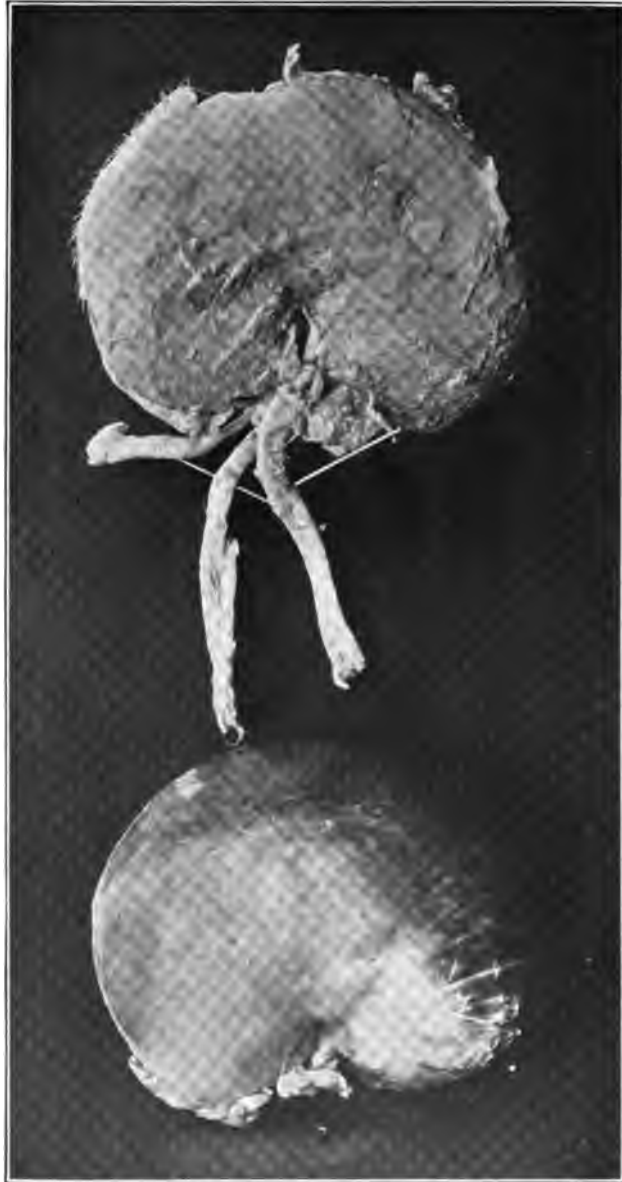
Fig. 75.—(Dog B949.) Upper specimen, transplanted kidney which has become infected. The sites of venous and arterial anastomosis are indicated at the positions pierced by pins. Note the continuity of caliber and gross structure at these points. Lower specimen, right kidney. The dog lived seventeen days.

Fig. 76.—(Dog B949.)   Branches of second cervical nerve which have become intimately attached to a newly formed outer capsule.   Enlarged about two diameters.
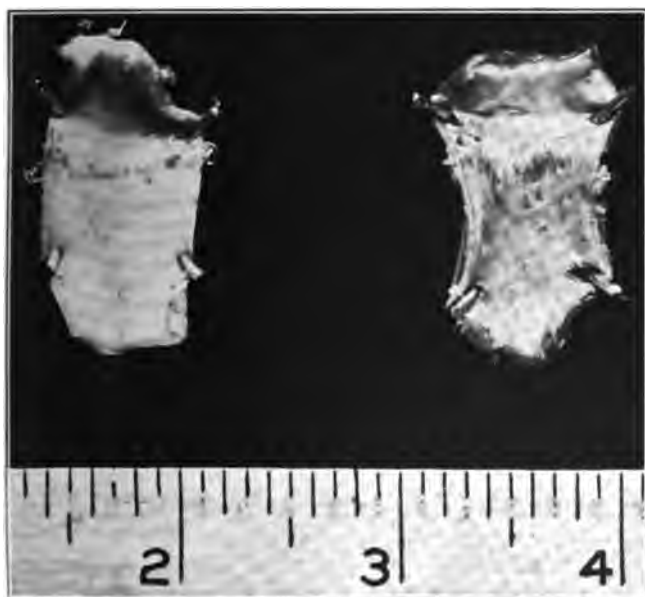
Fig. 77.—(Dog B949.)   Inside appearance of the renal vein and artery at the sites of anastomoses.   Continuous endothelium is shown, but there still remains suture material, shown at the sectioned edges and buried in the thickness of the vessel wall seventeen days after the transplantation.

Fig. 78.—(Dog N976.)　Twenty-four hours after right nephrectomy.

Fig. 79.—(Dog B976.)　Three months and sixteen days after operation.

Conclusions

1. It is possible for a dog to remain alive and in good health more than four months after the transplantation of one kidney to the neck, even when the remaining kidney is removed two weeks after the transplantation.

2. After the transplantation of a kidney with its ureter the ureter may be seen to move when contracting during excretion.

3. The ureter in a renal transplant may have the power to squirt the urine away from the animal by periodic contractions.

4. Phenolsulphonephthalein may return in four minutes from a transplanted kidney.

5. Many branches from the second cervical nerve may, in seventeen days, become intimately incorporated in the perirenal tissues of a cervical renal transplant.

6. The quantity of urine from a cervical renal transplant is markedly increased after the removal of the other kidney.

7. The neck is a favorable site for the observation of an experimentally transplanted kidney and its excretion.

REFERENCES

1. Borst and Enderlen: Über Transplantation von Gefässen und ganzen Organen. Deutsch. Ztschr. f. Chir., 1909, xcix, 54–163.
2. Carrel, A.: The surgery of blood vessels, etc. Bull. Johns Hopkins Hosp., 1907, xviii, 18–28.
3. Carrel, A., and Guthrie, C. G.: Functions of a transplanted kidney. Science, New York, 1905, n. s., xxii, 473.
4. Floresco, N.: Recherchés sur la transplantation du rein. Jour. de physiol. et de path. gén., 1905, vii, 47–59.
5. Guthrie, C. G.: Blood vessel surgery and its applications. New York, Longmans, 1912, p. 120.
6. Ullmann, E.: Experimentelle Nierentransplantation. Wien. klin. Wchnschr., 1902, xv, 281–282.
7. Villard, E., and Tavernier, L.: La transplantation du rein. Presse méd., 1910, xviii, 489–492.

SUPERNUMERARY AND SINGLE URETERS OPENING EXTRAVESICALLY*

E. S. JUDD

The ureter arises as a process from the posterior wall of the lower end of the Wolffian duct. Its distal end divides normally into two branches, which grow into the blastoma of the kidney. Each branch then divides and subdivides and forms the straight and uriniferous tubules and calyces. Early in embryonic life the proximal end of the ureter opens into the lower end of the Wolffian duct, but under normal conditions, at about the sixth week, the ureter and duct separate and open separately. If the ureter does not become detached from the duct and accompany it in its downward course, the ureteral opening may be found in any one of the organs developing from the urogenital sinus. If the Wolffian duct and the ureter fail to shift before the urorectal septum forms in the cloaca, the ureter opens into the rectum. Apparently this condition is very rare; I have not been able to find it mentioned except in reports of fetuses otherwise abnormally developed. If the ureter continues its association with the Wolffian duct, it empties into one of the organs developed from the duct, such as the vas deferens, seminal vesicle, ejaculatory duct, or Gartner's duct.

Furniss has reported a case of supernumerary ureter with an extravesical opening. He abstracted an article by Hartmann, of Copenhagen, who has analyzed 37 cases collected from the literature, 14 of which were supernumerary. In these 37 cases the extravesical openings were distributed—6 in the urethra, 8 in the vagina, 21 in the vestibule of the vagina, and 2 in Gartner's duct. Hartmann's review shows that the abnormal opening, whether from a single or from a supernumerary ureter, most often occurs in some part of the vagina. In such cases in the embryo the ureter maintains its connection with the Müllerian or Wolffian duct. However, it very seldom empties into the Fallopian

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tube or uterus. Such abnormalities are reported to have been found in the fetus in a few instances.

If the ureter does not become separated from the Wolffian duct, the opening may occur in the urethra or in the vestibule of the vagina, and apparently this is the embryonic abnormality which occurs most frequently.

It is possible that this abnormality is much more common than we are led to believe from the cases reported in the literature, and may be explained by the fact that it is usually very difficult to make a diagnosis of the condition, even though the clinical features are almost always suggestive. The 37 cases reported by Hartmann apparently included all the cases in the literature at that time (1913). In 14 of these the opening was that of a supernumerary ureter; in the remaining 23 the ureter was single or the exact condition was not determined. Furniss also abstracted an article by Hartmann, of Leipzig, who had collected 16 cases of positive supernumerary extravesical ureters, 12 cases of uncertain supernumerary extravesical ureters, and 7 cases of a single ureter opening extravesically.

Kelly and Burnam describe one case in which a single ureter opened into the urethra; five other observers reported cases of a single ureter opening into the vagina, and three reported cases of supernumerary ureters with openings in the vagina. Peacock reports a necropsy on a child nine months old that had four ureters, one of which terminated in the vesicoprostatic urethra.

I wish to add to the cases in the literature reports of two cases: one in which a single ureter opened into the urethra, and one in which the supernumerary ureter opened into the vagina.

A clinical history of constant incontinence of urine, associated with periods of normal urination, suggests the existence of a ureter with an opening outside the bladder-sphincter. Such a history was characteristic of both of our cases. In the patient having a supernumerary ureter this history had been constant from birth up to eighteen years of age, at which time she was operated on elsewhere and obtained complete relief. Her symptoms returned six years later during her first pregnancy, although the incontinence was not so regular or typical as it had been previously. For several days and sometimes for weeks there would be no leakage, when she would have a period of incontinence. Following delivery her condition improved and during her second pregnancy the symptoms returned and persisted until she was operated on.

'17—14

Our second case was that of a girl twenty-two years of age. The ureter opened into the urethra, and she had had incontinence as long as she could remember. There is one point of unusual interest in the history of this patient; apparently for long periods there would be no leakage at night and at times no soiling during the day. We were unable to explain this until at operation a greatly dilated and thickened ureter was found, which seemed to indicate that it had been obstructed at times and that there was considerable infection in its walls. Infection was naturally to be expected in this type of ureter, in spite of the fact that the urine collected before operation showed only a small amount of pus. Soon after operation a large amount of pus was found in the urine, but this gradually cleared up. Before operation the patient had three attacks of acute pain in the right side, probably due to an inflamed appendix, although it was possibly caused by the infection in the kidney and ureter.

In addition to these two cases, a number of cases of urinary incontinence have been treated, especially among young girls, in which we were not able to determine the etiology. In some the condition was probably due to a low-grade inflammation of the bladder, obscure nervous disorder, or to a relaxed bladder sphincter, very uncommon among young unmarried women. It is also possible that in some instances the incontinence was due to a ureter with an extravesical outlet, although the opening could not be located at the time of the examination. In our examinations in order to locate the abnormal opening, we have employed methods very similar to those described by Furniss.

The suggestion of a single ureter is substantiated by a cystoscopic examination which shows the absence of the other. In our case the ureter was located very close to the bladder-sphincter, but it could be seen distinctly. Even if there is a supernumerary ureter, the cystoscopic examination may reveal a normal bladder with normal meatuses and normally functionating kidneys, as in one of our cases. If an extravesical opening is suspected and cannot be located, we have found it helpful to place pledgets of cotton in the vagina and urethra and over the meatus of the urethra, and to inject subcutaneously and intravenously some sort of dye which colors the urine as it is eliminated. If the extravesical opening does not discharge continuously, it may be necessary to repeat the procedure several times.

Treatment consists of implanting the truant ureter into the bladder. This has been done in several ways, most often, I think, by vaginal

)peration.   In some instances a small sac has been found at the lower
ₑnd of the ureter and has caused some difficulty in the performing of the
)peration.

In the case of the supernumerary ureter herein described, Dr. Maxon
of California had previously performed a vaginal operation.   The ureter
had been freed in the vagina, an opening made in the bladder over a
sound, and the ureter drawn into it.   The operation had completely
relieved the patient and undoubtedly she would have remained well if
changes had not been produced by the pregnancies some years later.
The stretching of the tissues had altered conditions so that at the time
of our examination it was impossible to determine the area of implanta-
tion.   We felt sure that this ureter had been closed continuously for
long periods and that it would be very difficult to reimplant it on account
of the scar, therefore the supernumerary was ligated with satisfactory
results.

Under ordinary circumstances, however, it is my opinion that the
procedure of choice is the abdominal extraperitoneal implantation of the
abnormal ureter.   This was done very satisfactorily in our second case
in spite of the fact that there was considerable infection in the ureter.
The technic of the abdominal operation is more accurate and the implan-
tation may be made with a better chance of preserving the lumen of
the ureter and, therefore, the function of the kidney.   We have suf-
ficient evidence to show that ureters transplanted in this manner will
continue to functionate and maintain a normal kidney-function over a
number of years.   We have recently examined two patients in whom
the ureter had been transplanted four years previously and in both
instances the adjoining kidney was practically normal.   In our two
cases under discussion the incontinence was relieved immediately and
relief has been permanent.

CASE A163923.—M. L., a single woman, twenty-one years of age,
first consulted us June 27, 1916.   The menstrual history was normal.
She complained of diurnal enuresis which had troubled her all her life.
She had had nocturnal enuresis when she was younger but not recently.
She complained of constipation and stated that when her bowels moved
freely or following physic, she had very little or no trouble.   The drib-
bling of urine was not constant, but strain or excitement caused it to
escape.   Previous to one year before examination she had had three
attacks of sharp, colicky pain in the right side of the abdomen, each of
them lasting from one to two days.   The attacks of pain were followed
by soreness, and the physician who saw her in the attacks told her they

were due to appendicitis. In repeated examinations of the urine considerable pus was found, and cystoscopic examination showed some inflammation in areas at the left base. The ureteral meatus on the right side could not be found; the left meatus, situated just inside the internal sphincter muscle on the left side, appeared to be entirely normal, and clear urine was seen coming from it. The bladder-sphincter was apparently relaxed, and it was thought that this might account for the incontinence (Figs. 80 and 81).

Operation.—The sphincter was tightened by folding it upon itself and by taking a few stitches, but this did not relieve the symptoms.
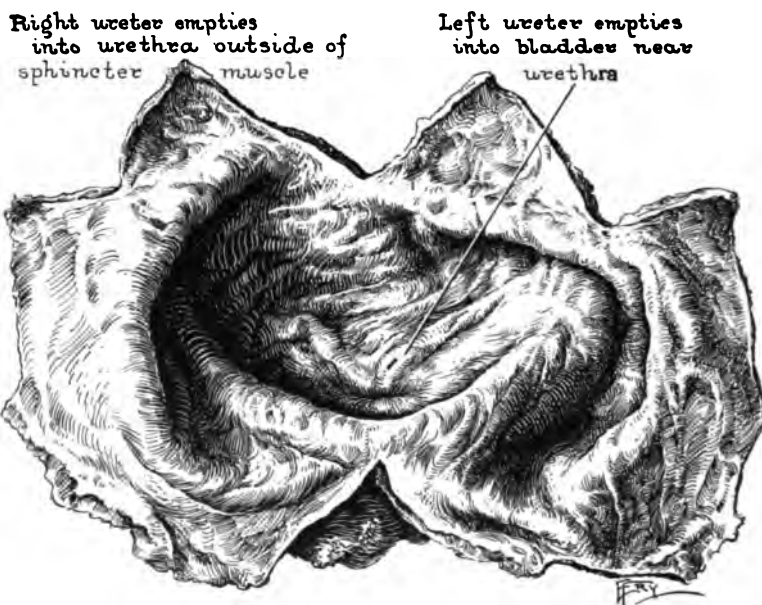
Fig. 80.—Probable appearance of a bladder having only one ureteral meatus near median line and just above urethral sphincter.

Ten months later the patient returned for an examination, at which time her history was typical of extravesical ureter. She had incontinence and dribbling of urine, and in addition voided normally from three to five times daily. It was necessary for her to wear a pad constantly.

Cystoscopic examination at this time showed a left ureteral meatus situated just inside the bladder sphincter. On withdrawing the cystoscope an apparently normal meatus was found in the right wall of the urethra, $1\frac{1}{2}$ cm. outside the bladder sphincter. The right ureter was normal in length. The right ureter was exposed through a right rectus extraperitoneal incision. The ureter was greatly dilated and thickened.

It was surprising to find such marked infection in the wall of the ureter, which, of course, was positive indication that the kidney was infected. However, we decided to implant the ureter and, if necessary, to perform a nephrectomy later.

A few days after the operation the patient had considerable pain in the region of the right kidney and there was pus in the urine.   Two
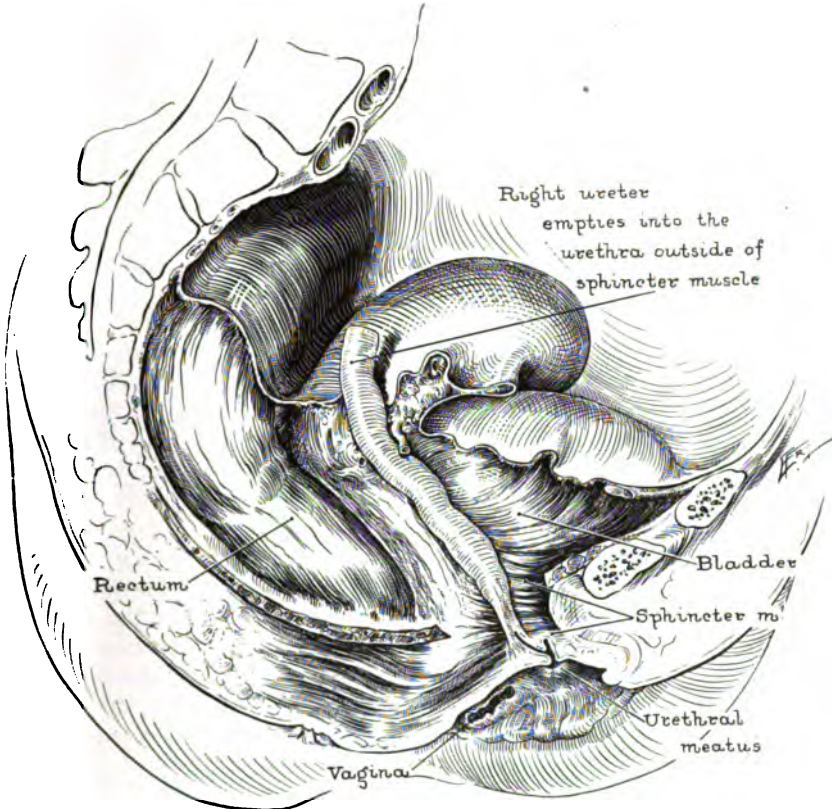
Fig. 81.—Single ureter on right side was markedly dilated and had a thickened wall.   This ureter opened into the urethra posteriorly, 1.5 cm. below the sphincter muscle.

ureteral catheters were readily passed into the pelvis of the kidney, and continuous pelvic lavage was instituted.   From this time on the pain decreased.   The wound healed promptly, although there was slight urinary drainage from it for a few days.   The incontinence ceased after the operation, and she has had no further trouble of that nature, although at times there has been evidence of pyelonephritis, such as pain in the side and an occasional slight chill.   Repeated cystoscopic examinations have been made, and the kidney pelvis has been irrigated.   At the present

time, eighteen months after operation, the patient is practically free from symptoms, and will probably not require nephrectomy. The functional capacity of the right kidney is only about half that of the left.

CASE A177181.—J. T. R., a woman forty-eight years of age, who had been married seventeen years. She had two children, sixteen and thirteen years of age. The menopause had occurred three years previously. This woman came for examination because of urinary drainage from the vagina; from birth she had had partial incontinence. When eighteen years of age, she was operated on for this trouble by Dr. Maxon. In a communication from Dr. Maxon he states that a congenital truant ureter was found at operation. The right ureter passed just under the anterior vaginal membrane, but had no connection with the bladder and came out very near but not in common with the lateral meatus of the urethra at the time of the operation. The patient was dribbling about half the urine. Dr. Maxon dissected the ureter from the external opening for about 2½ inches up the anterior vaginal wall. He then cut away about 2 inches of the ureter, passed a sound into the bladder, and made an opening in it about where the ureter would normally enter. After placing one stitch in the lower end of the ureter, fully one-half inch of it was pulled into the opening made in the bladder and sutured there. The vaginal wall was closed. In a few days the redundant portion of the ureter came away and an uneventful recovery followed (Figs. 82 and 83).

This operation was performed twenty-two years previous to our examination, and the patient was entirely relieved until her first pregnancy, when about the fourth or fifth month of gestation the incontinence returned. It was not so constant, however, except when she was on her feet. During the second pregnancy she had a greater degree of incontinence. When she was first examined at the Clinic, the trouble varied; it was worse at times, but there was some incontinence most of the time.

On several examinations of the urine small amounts of pus were found. The cystoscopic examination was negative. Both ureteral meatuses appeared normal, the individual phenolsulphonephthalein output was normal, and there was no evidence of the supernumerary ureter in the bladder. There was unquestionably some escape of urine into the vagina, although it was difficult to determine where it was coming from.

Operation.—A small incision into the scar of the former operation led into a little pocket which seemed to contain urine, but it was impossible to pass a probe through the pocket into the bladder; it could only be passed about one-half inch. The sac was stitched over, and apparently the condition was relieved. However, the relief was only temporary, and in a few weeks there was a greater amount of drainage than pre-
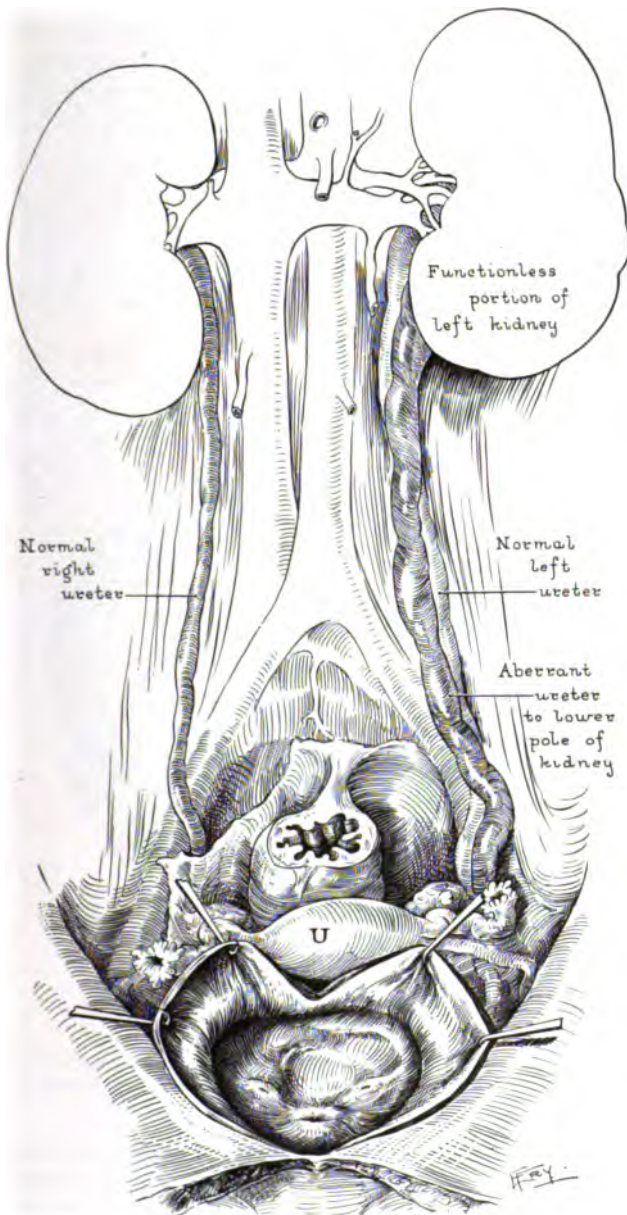
—Normal bladder with two ureters and meatus in the left side. The aberrant ureter crosses the normal
at two distinct points. The supernumerary ureter probably drains the upper pigment of the kidney.

viously. Some months later we succeeded in passing a probe into the
pouch for several inches, but it did not pass into the bladder. We
again dissected out the fistulous tract, and found that it led to a super-
numerary ureter which was strictured about two inches from the opening.
There was some dilatation above this point.   There was a great deal of
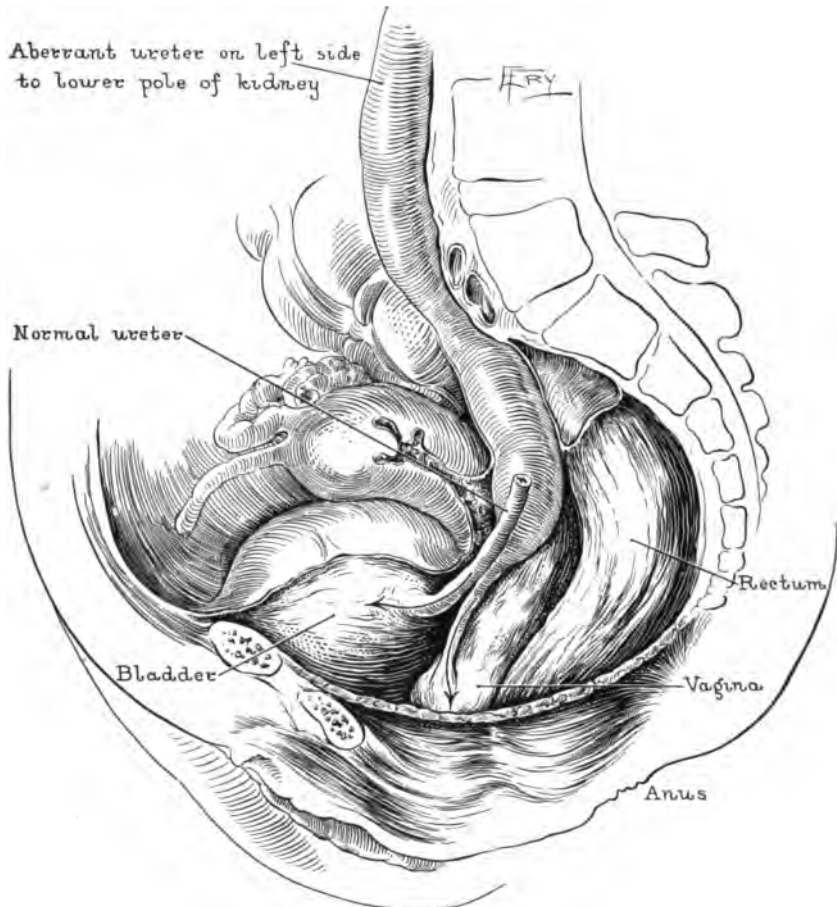
Fig. 83.—The lower ends of the normal and supernumerary ureters. The supernumerary ureter was normal in its diameter for one and one-half inches where it became markedly dilated as far as could be determined.

scar tissue due to the former operations.   The ureter had undoubtedly
been closed previously for long periods, and it was probable that the
adjoining kidney-tissue was destroyed.   It seemed safe to ligate the
ureter, and this was done with complete and permanent cure of the
incontinence.

After the operation the patient had some increase in temperature

which lasted for several days. There was little or no pain in the region of the kidney and no other evidence of trouble from the ligation of the ureter.

REFERENCES

1. Hartmann, J. P.: Zur Kasuistik und operativen Behandlung überzahligen aberranter Ureteren. Ztschr. f. Urol., 1913, vii, 429–446.
2. Hartmann, J. P.: Ueber die extravesikale Ausmündung der Harnleiter bei Frauen. Ztschr. f. gynäk. Urol., 1913, iv, 69–88.
3. Furniss, H. D.: Supernumerary ureter opening intravesically. Surg., Gynec. and Obst., 1914, xviii, 584–586.
4. Kelly, H. A.: Diseases of the kidneys, ureters and bladder, with special reference to the diseases in women. New York, Appleton, 1914.
5. Peacock, A. H.: Multiple ureters with hydronephrosis. Jour. Am. Med. Assn., 1916, lxvi, 1088–1089.

CONTUSION AND RUPTURE OF THE KIDNEY*

E. S. JUDD

Contusion and rupture of the kidney occur more frequently in men, as they are more frequently subjected to violence which produces this kind of an injury. In women the kidney is much better protected by the iliac crest and clothing, and it has a greater amount of mobility and perirenal fat. Contusion and slight rupture of the kidney probably occur more often than is realized, as in many instances recovery is spontaneous and a physician may not have been called. Küster, in a review at his clinic of 7740 injuries, reports 10 cases of injury of the kidney. Israel, in his large clinic in Berlin, has had but 1 operative case. Keen's analysis of 155 so-called injured kidneys shows that 118 were subcutaneous ruptures and 2 were ruptured ureters. In our series of cases I was able to find 10 injured kidneys and ureters. In 8 of these cases operation was done and the diagnosis proved. The other 2 were diagnosed clinically only, as the patients recovered without treatment.

Such injuries are usually the result of violent blows directly over the kidney. Occasionally the blow drives the kidney against the lower ribs or transverse processes of the first and second lumbar vertebræ. When a person falls from a great height, the kidney may be injured by a sudden concussion of the body or by an abrupt flexion. According to Küster, the mechanism of producing the injury in most cases is force, hydraulic in nature, acting through full vessels and a full pelvis. Any force acting on the kidney under such circumstances causes it to burst along the lines radiating from the hilum in the direction of the tubules. The distended organ, driven against the spine by the impact of the ribs, will tend to tear at the point of maximum impact. There is usually very little or no external evidence of injury. In our ten cases there was no superficial evidence of injury.

A study of morbid anatomy shows that in contusions blood is extravasated into the perirenal fat or into the parenchyma, and passes down

* Presented before the American Railway Surgeons Association, Chicago, Oct. 18, 1917. Reprinted from Rail. Surg. Jour., 1918.

the urinary tubules into the pelvis of the kidney. In rupture of the kidney deep fissures extend through the capsule and parenchyma, and often into the pelvis. Sometimes the kidney is completely torn across. This occurred in three of our cases, and it was necessary to remove the kidney in separate pieces. The hemorrhage is severe in such cases, the blood extending widely through the perirenal and retroperitoneal fat. If the ureter is intact, some of the blood will pass down into the bladder. If the peritoneum is lacerated, as it is in some of these cases, a large amount of blood may escape into the abdominal cavity. This occurred in one of our most severe cases, and a large number of clots were wiped out of the open peritoneum. If the rupture extends completely through the substance of the kidney, the urine will escape with the blood into the surrounding tissues, adding the element of infection to the hematoma and producing a much more serious condition. In six of our eight patients operated on the kidney was completely ruptured and there was a great quantity of urine and blood in the perirenal tissues.

Rupture of the renal artery is sometimes seen. This apparently had occurred in one case in our series, and had been classified as a spontaneous rupture of a pathologic kidney. The hematoma in this case was of a tremendous size, and as soon as the clots were loosened, free bleeding occurred from the renal artery. There was no evidence of an aneurysm of the vessel, and there was not enough infection to produce a slough through the wall of the vessel. In all probability this was an instance of rupture of the renal vessel.

Avulsion of the ureter occurred in two of the patients operated on. Both operations were done some weeks after the injury, and in both efforts were made to locate the ureter. There was considerable infection in both instances, and abscess pockets with considerable granulation tissue filled the spaces of the pelves. No sign of a ureter was seen in either case. No hematuria occurred at the time of the accident or subsequently.

The greatest danger in case of rupture of a kidney is from hemorrhage. Shock, often very marked, is probably owing to the sudden loss of a large amount of blood, which may be sufficient to cause death. In one such case in our series the man was pulseless for some time and it was thought he could not survive. After about twelve hours, however, he gradually reacted and a little later was operated on and recovered. I am convinced that if we had attempted to operate at the height of the shock and hemorrhage, the patient would not have survived.

Infection is the factor of second importance in these cases. It usually becomes noticeable about forty-eight hours after the injury. If the rupture does not extend into the tubules and pelvis, it is possible that infection will not occur; the blood will be absorbed and the wound in the kidney will heal spontaneously. This apparently took place in our two cases in which operation was not performed. A positive diagnosis could not be made, but the fact that bleeding occurred from the kidney shortly after the injury is certainly suggestive of rupture. The laceration was probably slight, and there was only a small amount of bleeding. There was no infection, and the wound in the kidney healed promptly. In 4 of our 8 cases large abscesses had formed (1 in two weeks; 1 in three weeks; 1 in four weeks; 1 in seven weeks) and it was deemed advisable to drain them, with a view to the possibility of saving the kidney, and because it seemed the safer procedure on account of the amount of infection. However, in all four of the cases it was necessary to remove the kidney later.

The clinical features presented in such cases are usually, first, a picture of profound shock, and second, a reaction with nausea, vomiting, and pain in the kidney area, often radiating to the thigh and testicle. The patient may also have a typical renal colic, caused by clots passing down the ureter. There is seldom any evidence of bruising of the soft tissues over the kidney. Soreness and tenderness in the loin are always present even in cases of slight rupture. The abdominal muscles on that side are rigid, and tympanites may be marked. Hematuria is the most constant symptom, and is present in all cases except those in which a clot obstructs the ureter or the ureter is torn off. The hemorrhage in two of our cases was severe. In some cases it has been fatal. In most instances it is intermittent, lasting for a few days, clearing up entirely for a short time, and then reappearing. This may be repeated several times. Swelling in the loin occurs in nearly all cases, and is due to the accumulation of urine and blood. In some of our cases it appeared as a large tumor, filling the entire injured side of the abdomen. If the capsule has remained intact, it may become distended and present a large, tender, movable mass. Uremia is rare. Usually, after about forty-eight hours, septic changes occur and perirenal infection is evidenced by chills and irregular temperature. At this time the urine will contain a large amount of pus. In all our infected cases the infection occurred as a walled-off abscess; however, in some reported cases it resulted in a diffuse cellulitis extending into all the surrounding tissues.

The following are tabulated data of our cases as to the age, the nature

of the injury, the chief symptoms, the time of treatment, and the condition in which the kidney was found at the time the patients were operated on.   All these patients recovered.

TABLE 1

CASE	AGE	NATURE OF INJURY	CHIEF SYMPTOMS
1	11	Kicked by a horse.	Hematuria, tympanites, pain, soreness, lump.
2	29	Fell through a floor.	Hematuria, pain, tenderness, infection, sinus.
3	5½	Run over by a buggy.	No hematuria, shock, vomiting, pain, swelling, sinus.
4	36	Fell over a small wagon.	No hematuria, pain, severe chills, fever, tender swelling, infection, no urine from the injured side.
5	65	Spontaneous rupture.	Hematuria, shock, tender tumor, vomiting, severe pain.
6	7	Struck by auto.	No hematuria, swelling, septic sinus, complication with fractured skull.
7	11	Fell down-stairs.	Hematuria, vomiting, tender swelling, no secretion from the injured side, sinus.
8	33	Runaway accident.	Hematuria, intermittent chills and fever, tenderness, rigidity, clots in the bladder, no secretion from the injured side.
9	46	Strained lifting a heavy block of ice.	Hematuria for eight days, some soreness over sacral spine.
10	34	Fell three feet onto cement sidewalk, then rolled over a barrel.	Hematuria, pus in the urine, severe pain in the right kidney region and testicle.

TABLE 2

TIME OF TREATMENT	CONDITION
1. Nephrectomy two weeks after injury.	Complete rupture dividing kidney into two parts; lower half gangrenous.
2. Examined within twenty-four hours. Patient apparently recovering. Abscess drained after two weeks, nephrectomy after seven weeks.	Large abscess, kidney completely divided into two parts.
3. Abscess drained three weeks after injury, nephrectomy six weeks after injury.	Complete rupture; kidney removed in two separate pieces.
4. No pain for two days after the injury, nephrectomy three weeks after the injury.	Small abscess; kidney not ruptured; ureter completely severed from the pelvis of the kidney.
5. Immediate shock, nephrectomy in about three days.	Complete rupture of pathologic kidney, bleeding from vessels in the pedicle, large hematoma.
6. Abscess drained one month after the injury, nephrectomy more than two months after the injury.	Much cellulitis; the kidney not ruptured although the ureter and pelvis were completely separated.
7. Abscess drained seven weeks after the injury, nephrectomy one year after the accident.	Complete rupture, huge hematoma, and ureter obstructed.
8. Nephrectomy more than two weeks after the accident.	Complete transverse and longitudinal rupture of the kidney.
9. Cystoscoped elsewhere about the sixth day; cystoscoped by us five weeks after the accident. Findings negative.	
10. Physical examination five days after the accident; no other procedures.	

The treatment to be employed is determined by pain, shock, and hemorrhage. If the local symptoms are insignificant, the constitutional symptoms slight, and hematuria is not marked, expectant treatment may be instituted. The 2 patients in our series not operated on undoubtedly had ruptured kidneys and yet both recovered completely without treatment. In one the hematuria, which was not severe, lasted about eight days. This patient was cystoscoped five weeks after the injury and both kidneys were found apparently normal. The same patient was cystoscoped on the sixth day after the injury, and blood was seen coming from the traumatized side. It is possible that because some of the slightly injured kidneys have healed spontaneously, we have carried the expectant treatment too far in other cases. Operative interference is surely indicated if there is an increasing loss of blood or if there is evident involvement of the peritoneum. In spite of the fact that the patient's condition may be very grave, surgery probably offers the only chance. If the swelling in the loin is increasing or the amount of urine is diminishing, an exploration should be made.

In some of our cases an earlier exploration might have saved the kidney. After infection has taken place it is not possible to pack the rent in the kidney or clear away the clots and suture the wound with any degree of success. However, if the kidney is inspected before infection has occurred and it is found to be viable and not too extensively lacerated, it would seem that the procedure of choice is loosely to suture the parts together and drain the wound freely. If the kidney is extensively lacerated and the vessels are ruptured, or if the ureter is torn away, it will then be necessary to remove the kidney.

Reports of Cases

Case 1 (60578).—A. D., a boy eleven years of age, was examined October 26, 1911. Two weeks previously the child had been kicked in the left lumbar region by a horse. For a week there was marked tympanites; temperature, 104 to 105 F. Blood passed from the bladder for several days and then stopped. However, for a week he had been passing blood with the urine. At first pain was severe over the left kidney area, but was relieved by strapping. A large lump had been noticeable in the left side of the abdomen since shortly after the injury. At the time of the examination there was some soreness. The urethra was small, and a cystoscopic examination was not possible.

Operation eighteen days after the injury. Through a posterior incision the huge lump was exposed, which proved to be a ruptured

:idney with perinephritic hematoma and infection. The kidney was plit in the middle. The lower half was gangrenous; the upper half ad some nourishment, but the capsule was filled with infected urine. hese fragments of kidney tissue were removed. The recovery was neventful (Fig. 84).

CASE 2 (86559).— I. S., a girl five and one-half years of age, was amined June 24, 1913. Six weeks previous to the examination the ild had been run over by a heavy buggy, the hind wheel passing over the abdomen. Following the accident she had severe pain, a high pulse, obstruction of the bowels, and profuse vomiting for several days—blood on one occasion. Recovery then seemed to take place. Three weeks later the whole left abdomen became swollen and the temperature and pulse indicated infection. An incision made by

4.—Case 1. Ruptured left kidney with
rinephritic hematoma and infection.

Fig. 85.—Case 2. Ruptured left kidney.

al physician revealed a retroperitoneal mass. Thirty-four ounces of d and urine were drained, and in a day or two the discharge consisted ear urine. After this the child had been comfortable with drainage, when this stopped there was pain. The physician wrote that methyblue injected into the sinus did not show in the bladder. At the time ir examination the child's general condition was good. There was ess in the left kidney area. A subcutaneous injection of indigo-in drained partly through the sinus. The x-ray examination was

negative. The urine showed a specific gravity of 1010 and was negative except for an occasional red blood-cell and a little pus.

At operation (C. H. M.) the left kidney was shown to be completely ruptured, and it was removed in two separate pieces. A sinus persisted for some time, but recovery was eventually complete (Fig. 85).

CASE 3 (179949).—Mrs. A. P., a female thirty-six years of age, came for examination December 6, 1916, because of pain in the right kidney region. A week before coming to the Clinic she had stepped out in the dark and had fallen over a little express wagon. She did not realize that she was hurt, but two nights later severe right-sided pain developed, with vomiting and urinary frequency. Since then she has had almost constant pain and soreness in the region of the right kidney. She has also had chills and fever, followed by sweats in the evening. There has been loss of appetite and strength. No history of hematuria. The physical examination was negative except for a tender enlargement in the right kidney region. Cystoscopic examination demonstrated that there was no urine coming down from the right side. The left side was normal. Phenolsulphonephthalein showed on the left side in four minutes, and 25 per cent returned in

Fig. 86.—Case 3. Perinephritic infection about the lower pole (right kidney).

fifteen minutes. The x-ray examination was negative. Diagnosis: Functionless right kidney and probably traumatic rupture. The history of injury was so slight that the patient was kept under observation for two weeks before the diagnosis seemed positive enough to warrant operation. Repeated examination of the urine at this time showed albumin 2 and only a few pus-cells. The leukocyte count was 25,800. The temperature was intermittent—at one time nearly 105 F.

The operation revealed a great deal of perinephritic infection about the lower pole, very little pus, but necrosis and granulation tissue. The

1ey was adherent and had many small abscesses throughout the
ex. The infection extended through the pelvis, and the ureter
ld not be found. The ureter had apparently been completely
·red from the pelvis, or had sloughed off during the extension of the
ction (Fig. 86).

ᴄᴀsᴇ 4 (83188).—N. E. F., a man twenty-nine years of age, was
nined April 22, 1913. Twenty-four hours before the examination
patient had fallen through a hole in a floor in such a way that his
·r left chest struck the edge of the hole. He lay for fifteen minutes
.use of the pain in his side, which gradually grew worse until it
.me excruciating. Five hours after the injury he passed a large
unt of blood in the urine, which relieved the pain a great deal.
r that he passed only a small amount of blood and had no pain
1 he was quiet. The urine ex-
ied while he was under observa-
showed some blood. He gradu-
recovered and was able to be up
around. The urine was clear
of the time, but there was a
t rise in temperature occasion-
The patient left the Clinic, but
ned in six days with an increase
in and tenderness over the left
·y area. Micturition was pain-
id there was considerable pus in
rine.
n exploration was made, and a
perinephritic abscess drained.
weeks later a cystoscopic exam-
in showed that there was no
ion in the left kidney. Seven
; after, the kidney, which had
completely divided by the in-
was removed in two separate

Fig. 87.—Case 4. Perinephritic abscess of left
kidney.

; (C. H. M.). The patient recovered promptly and has remained
Fig. 87).

ᴠsᴇ 5 (156050).*—E. E. T., a man sixty-five years of age, was
ned March 29, 1916. Fifteen years previously the patient had
ain in the left kidney region. He consulted a physician and was
medicine, which relieved him. He had no further trouble until
.ly, when on shoveling coal into the furnace he coughed and
d. This was followed instantly by severe pain in the left loin and
nen, which continued until the examination twelve hours afterward.

'his case has been reported by Dr. G. J. Thomas: Spontaneous or non-traumatic
: of the left kidney. Journal-Lancet, 1917, xxxvii, 84–86.

'17—15

The urine had become bloody, and each specimen had been very dark with blood. He vomited several times. There was a large and very tender mass in the left kidney region. The patient appeared anemic. The systolic blood-pressure was 230, the diastolic, 110. Urinalysis showed a large amount of blood and a small amount of pus. The x-ray showed shadows in the left kidney area. Because of the patient's condition no further examination was made. The tumor in the region of the kidney was increasing, a diagnosis of spontaneous rupture of a pathologic kidney was made, and an operation was performed immediately (E. S. J.).

Incision through the superficial tissues showed a very large hematoma containing at least two quarts of clots and fluid. As soon as this was cleared out very free arterial bleeding was observed coming from the kidney pedicle. The pedicle was caught in clamps, and the large hydronephrotic and cystic kidney was removed. Stones were present, and there was almost complete destruction of the parenchyma. There was a large amount of blood and considerable fat in the dilated kidney pelvis. The patient made a good recovery, though the wound was slow in closing.

Fig. 88.—Case 6. Ruptured left kidney.

CASE 6 (202333).—J. R., a boy seven years of age, was examined July 20, 1917. This boy had always been well until June 2, 1917, when he was struck by an automobile moving at the rate of four to five miles an hour. He was unconscious for eight days. The right side of the skull was trephined elsewhere on June 5 for a depressed fracture, and almost complete motor paralysis of the left side. These symptoms cleared up within twelve days. About a month after the injury a tumor mass was discovered in the left kidney area, which grew rapidly and in the course of a few days he had several convulsions. The mass was opened by the local doctor, about one gallon of a serosanguineous fluid was removed, and the wound closed. Ten days later it was necessary again to aspirate the region. This time straw-colored fluid having the odor of urine was removed. Clear urine continued to drain from the sinus. He passes about 10 ounces of urine from the bladder in twenty-four hours. X-ray examination revealed a fracture of the base of the

skull and a trephine opening. The patient was anemic and frail and looked uremic. During the time he was under our observation he had periods of apparent complete cessation of kidney elimination.

As soon as his condition warranted it, exploration of the left kidney area was made (E. S. J.) and a rupture through the pelvis of the kidney was found. The kidney tissue was not torn, but there was extensive peri-renal infection and a swollen and edematous kidney, completely separated from the ureter. The ureter was not found. After the removal of the kidney the patient's general condition improved rapidly. The remaining kidney functionated normally and he recovered completely (Fig. 88).

CASE 7 (71678).—H. G., a girl eleven years of age, was examined August 6, 1912. Seven weeks previously the child had fallen down-stairs, injuring her right side severely. She vomited for two days, and passed bloody urine twice. The side was sore for two weeks. She had been in bed about three weeks after the accident when her mother noticed a swelling in the right side, which gradually increased in size. At the time of the examination, seven weeks after the accident, there was no pain or inconvenience except the lump in the right kidney region. This mass was tense, but not very tender. It seemed to extend through to the back, and dullness was continuous with the liver dullness. X-ray showed a dense mass but no shadow. Urine showed a specific gravity of 1025. Cystoscopic examination showed that there was no secretion from the right side for fifteen minutes, and an obstruction to the ureter near the kidney. The left kidney was apparently normal.

At operation (W. J. M.) a ruptured right kidney was found with a huge hematoma forming a large tumor filling the right side of the abdo-men. There were more than two quarts of bloody fluid. The kidney was lying posteriorly and above the mass, and the ureter could be felt lying free. It was thought best to drain the hematoma and endeavor to save the kidney. The patient was discharged in a few weeks in good condition, except for a urinary sinus from the wound. She continued to improve, although the sinus persisted. She returned in eleven months with the sinus discharging enough to soil three or four pads each day. Cystoscopic examination at this time showed that no urine was coming into the bladder from the right side, and that the left side was normal. A subcapsular nephrectomy was performed. The fistula was found to lead down to the ruptured kidney. There was complete obstruction of the ureter and an abscess pocket of considerable size. The patient made a complete recovery.

CASE 8 (40524).—G. L., a man thirty-three years of age, was ex-amined July 18, 1910. Sixteen days previously he had been in a run-away accident and sustained an injury to his left groin. The following day and for one week after there was blood in the urine. He felt better for a number of days, then blood reappeared in the urine and he had fever and chills. He was pale and anemic looking, temperature 101.5 F. The left abdomen and left kidney region were very tender and the

muscles were tense. Cystoscopic examination showed a large amount of blood coming from the left kidney. The right side was normal. There were organized blood-clots free in the bladder and protruding from the right meatus.

The operation revealed the kidney ruptured transversely and the lower pole divided longitudinally. The rupture extended through the capsule and parenchyma into the pelvis. Nephrectomy was performed (W. J. M.). The recovery was uneventful (Fig. 89).

CASE 9 (158983).—W. A. S., a man forty-six years of age, came for examination May 4, 1916, because of hematuria. He had been well up to five weeks previously, when he lifted a heavy piece of ice. The following day he noticed bright red blood in his urine. The bleeding continued for about eight days; he was then cystoscoped and told that he had a tumor of the right kidney. He went home to prepare for an operation, and the bleeding and other urinary symptoms stopped suddenly. At the time of our examination, five weeks after the injury, there was some soreness in the region of the sacral spine. There was no macroscopic blood in the urine. Microscopic examination revealed a considerable number of red blood-cells. The cystoscopic examination showed apparently normal secretion on both sides.

Fig. 89.—Case 8. Kidney ruptured transversely and lower pole divided longitudinally.

This patient unquestionably had a slight rupture of the kidney at the time of his injury. The torn surface, however, did not become infected, and the laceration healed primarily.

CASE 10 (178162).—J. S. K., a man thirty-four years of age, came to the Clinic November 18, 1916, for an x-ray examination of the right knee, which had been injured five days previously when he fell three feet, striking on a cement walk and rolling over a barrel. He immediately felt intense pain in the patella, which persisted. He noticed blood in the urine, and he had severe pain in the region of the right kidney and testicle. When examined, he still had some pain in the region of the right kidney. Urinalysis showed red blood-cells and some pus. The symptoms subsided gradually without treatment.

This patient unquestionably had a slight rupture of the kidney which healed primarily without treatment.

A REPORT OF BACTERIAL VACCINE THERAPY IN A SERIES OF PROSTATIC CASES*

H. C. BUMPUS

Following the appearance of the Cabot and Crabtree paper setting forth the favorable results obtained from the administration of colon vaccine in a series of eight prostatic cases, the procedure was adopted from time to time in the Mayo Clinic, but not until May, 1917, was it systematically carried out. At about this time also there appeared an admirable article by Sholly, Blum, and Smith on the therapeutic value of bacterial vaccine in whooping-cough, the authors stating that during the administration of the vaccine they were very enthusiastic as to the beneficial results. However, after their tables had been compiled and carefully compared with the controls, the results showed that the untreated patients had done, on the whole, better than those receiving the vaccine. Similarly, Whittington reported on 230 typhoid cases with careful controls, and, interestingly enough, he also felt confident of favorable results until his careful analysis disclosed again that the controlled patients not receiving the vaccine had done better than those so treated.

In undertaking our study it seemed advisable to give all the patients the vaccine for five months and then to compare the results with those obtained in the previous five months without the vaccine. Thus the element of coincident time would be sacrificed for that of greater numbers, and the result, we believed, would be more accurate. This also seemed just since the treatment of these cases is now routine and has not varied appreciably during the present year.

Further, to make the two series as synchronous as possible, all cases in which the so-called two-stage operation was done (that is, suprapubic drainage followed by prostatectomy) have been considered separately. Judd believes that, with the exception of a few selected cases requiring

very lengthy drainage to reëstablish kidney-function, better results are obtainable by means of the permanent urethral catheter than by the suprapubic stab. The former renders a good surgical procedure possible since there is no scar-tissue to interfere with ample exposure, thus permitting injection of the capsule, excision of the gland, suturing of the capsule, and the establishment of complete hemostasis with ease and precision. The operative field, as in other surgical procedures, is clear and accessible. On the other hand, in the presence of an old suprapubic sinus with its accompanying scar-tissue, such procedure is impossible, and the operation which is performed tends to become the finger enucleation of the past, with its lamentable lack of precision and total disregard of hemostasis. A permanent urethral catheter preoperatively also has the added advantage of rendering the patient accustomed to its presence and thereby makes its postoperative use less hazardous.

The routine preoperative and postoperative treatment in relation to the vaccine therapy may be readily understood by Table 1, representing a chart such as is used in our prostatic cases. Thus in parallel columns records are kept of the phenolsulphonephthalein, blood-urea, specific gravity, volume, and microscopic and residual urine, together with the blood-pressure, hemoglobin, and the amounts of vaccine given from day to day. The vaccine was administered twice a week in doses beginning with 50 million, increasing by multiples of 50 to a maximum of 500 million, and continuing throughout convalescence.

Considerable thought was given to the question of the relative merits of stock and autogenous vaccines. The autogenous vaccines seem to have the greater amount of literature to their credit. They are, of course, always fresher, and, on the basis of specificity, would seem to be superior. The stock vaccine, on the other hand, is within reach of the greater number of physicians, and is safer, since it is put out by the large laboratories under Federal license. Therefore, following the technic of Cabot and Crabtree, we used mixed colon vaccine prepared from various strains of colon bacillus isolated from different urines and prepared fresh once a week.

The administration was subcutaneous, and, with two exceptions, no untoward symptoms resulted. The majority of the patients complained of malaise with slight nausea and a little rise of temperature, during the first few inoculations. The reactions resembled those usually associated with the administration of typhoid vaccine. Some patients stated that they could feel no effect; the majority regarded it as a necessary evil

and complained most of the localized inflammatory reaction, which lasted one or two days but always wore off. In the two patients mentioned the reaction was marked enough to require abandonment of the treatment, but never was in any way alarming.

TABLE 1

PROSTATIC RECORD.

To determine our results, a comparison of the patients treated with vaccine with those not receiving vaccine must be made relative to the incidence of complications manifestly due to infection—namely, pyelonephritis, epididymitis, phlebitis, cystitis, and wound-infection. The

last two conditions it seems best to disregard, as both are almost universally present to a mild degree in such cases, and their relative severity is difficult to use as a matter of careful comparison.

Pyelonephritis is naturally our best criterion. The characteristic symptoms of malaise, accompanied for several days by gradually increasing fever, with chills and sweats and a subsequent decline, make it typical, and to one who has been long associated with patients who are having residual urine repeatedly removed, the so-called "reaction" can never be forgotten. Cabot and Crabtree have reported a series of cases in which the colon bacillus was obtained during such reactions, especially during the chills, in pure culture from the blood-stream. We attempted to repeat their experiments, and although blood was obtained from six patients, all within an hour of the onset of the chill and from two at its height, in no instance could a growth be obtained, our cultures always being sterile. Owing to the absence of Cabot and Crabtree in Europe, we were unable to ascertain wherein our technic differed from theirs, and so gave up further attempts to isolate the organism. Therefore, to prevent such reactions or to reduce their severity becomes the chief function of the vaccine, and its final sentence in the court of last appeal must be based largely on its ability to produce evidence that the incidence of pyelonephritis is lessened by its administration. It has long been known and fully realized that a patient having undergone such a reaction, although for the time greatly weakened, is a better surgical risk than one who has not. Therefore, a patient having had a reaction and being subsequently treated with colon vaccine, may well be likened to one having recovered from typhoid and subsequently receiving typhoid prophylactic treatment, unless the immunity conferred by an attack of pyelonephritis is only transient, as Cabot and Crabtree suggest.

Phlebitis and epididymitis have also been added, together with the length of preoperative treatment and of convalescence, but the main judgment must rest on the pyelonephritis incidence. It seems only fair to state that at the writing of this paper the results had not been compiled, that at first we were very enthusiastic, that subsequently we became skeptical, and that after the completion of Table 2, we discontinued the administration of the vaccine.

Thus it appears that in the series in which vaccines were given there were 5 per cent less of cases of pyelonephritis than the controls and 1 per cent more than all cases. However, it must not be concluded that the

vaccine has produced this decrease, for if the action of the vaccine were specific, a greater reduction than 5 per cent should have occurred and the incidence, as compared with all patients operated on, should have been less—not greater. This conclusion is further supported by the 10 per cent increase in the cases of epididymitis among patients that were treated compared with the controls.

TABLE 2.—PROSTATECTOMIES FROM JANUARY 1, 1917, TO NOVEMBER 1, 1917

	For all causes	For Adenofibromatous Hypertrophy		
		Receiving vaccine	Not receiv- ing vaccine	Two-stage operations
Number	105	49	24	12
Average age	63	65	67	62
Days prior to operation	31	38	23	279
Days of convalescence	34	32	37	28
Total days treated	65	70	60	307
Pyelonephritis	31%	32%	37%	..
Epididymitis	26%	35%	25%	..
Phlebitis	4%	4%	4%	..
Number of deaths in the hospital	2	1	0	1

A survey of the length of time the treatment was given is of interest in demonstrating that, although the convalescence of the patients not receiving vaccine is longer by five days, their entire time under treatment is shorter by ten days, showing that the greater the length of preoperative preparation, the shorter the convalescence. This fact is further emphasized in the two-stage series, when a preparation of several hundred days is given to patients who are the poorest of surgical risks and leads to a convalescence much shorter than the average. In the two-stage series no attempt was made to chart the incidence of infection because much of the patients' preoperative time was spent at their homes where accurate observation was, of course, impossible.

CONCLUSIONS

1. Immunity to pyelonephritis cannot be produced by means of mixed colon bacillus vaccine.

2. The administration of mixed colon vaccine does not markedly reduce the incidence of genito-urinary infection, if it affects it at all.

3. Preoperative attacks of pyelonephritis are the natural means of

producing an immunity to renal infection, and their occurrence make
operative risks less.

   4. The length of convalescence is usually in inverse proportion to the
length of preoperative treatment.

REFERENCES

1. Cabot, H., and Crabtree, E. G.: The etiology and pathology of non-tuberculous renal
   infections. Surg., Gynec. and Obst., 1916, xxiii, 495–537.
2. Crabtree, E. G., and Cabot, H.: Colon Bacillus pyelonephritis—its nature and possi-
   ble prevention. Tr Sec. Gen.-Urin. Dis., Am. Med. Assn., 1916, 209–219.
3. Judd, E. S.: Surgical treatment of the prostate. Pa. Med. Jour., 1917, xxi, 72–75.
4. Von Sholly, A I., Blum, J., and Smith, L.: The therapeutic value of pertussis vaccine
   in whooping cough. Jour. Am. Med. Assn., 1917, lxviii, 1451–1456.
5. Whittington, T. H.: A report on the use of stock vaccine in infection by the Bacillus
   Typhosus. Lancet, 1916, i, 759–766.

INFECTIONS IN PROSTATE CASES*

E. S. JUDD

The importance of the preoperative treatment and the postoperative care of patients following prostatic operations is well established. A great deal has been done also to improve and simplify the operative technic, so that at the present time the operation is a much more definite surgical procedure than formerly. The element of infection in these cases has received due consideration, although apparently a great deal remains to be learned. In two seemingly parallel cases, one patient may have a very severe infection at any time following the operation. It is an accepted fact that the patient who has cystitis and other evidence of chronic infection at the time of operation is likely to be a better risk and is almost certain to have an easier convalescence than the patient who has a perfectly clean bladder and no symptoms of infection in the urinary tract. This would seem to suggest that the infection had produced a definite immunity, and further that some benefit might be expected from the preliminary use of vaccines.

In the majority of instances a very definite and characteristic reaction is brought about by preoperative treatment. Just what the etiologic factor of this reaction is has not been decided. It is characterized by general weakness, irritability, inability to rest, and loss of body weight. During the height of the reaction the specific gravity of the urine and other tests show that the function of the kidney is very much diminished. There is a marked reduction in the blood-pressure, which is usually high. After the reaction subsides all these symptoms disappear. The renal function apparently returns to normal, although the specific gravity of the urine will probably never reach the point of its first reading. During the reaction there may be much evidence of infection, such as chills, increased temperature, and pus in the urine, and in some instances blood cultures will be positive. This infection, if it is an infec-

tion, is characteristic. A patient well along in years will withstand a long abdominal operation under a general anæsthetic even though there is considerable infection in the operative field, and yet if at any time during convalescence this same patient has retention of urine so that catheterization is necessary for some time, there is almost sure to be more reaction from this procedure than from the abdominal operation. I do not believe we can accept the theory that the reaction which generally follows catheterization and the withdrawal of the residual urine is always due to infection alone. The reaction may occur at any time without any evidence of infection, and it would seem that it might be due to the change of pressure within the pelvis of the kidney, which permits a sudden congestion. This is turn interferes with the renal function.

In the somewhat detailed study of a small series of cases herewith presented an attempt has been made to ascertain as nearly as possible the part infection plays in the reactions which take place during the preparation of patients either by draining the bladder through a urethral catheter or through a suprapubic opening. It has been of interest also to find out just how often infection occurs during convalescence, and how much of a factor it is in the convalescence and in determining the mortality.

Infection in the kidney is the most important factor to be taken into consideration. The question arises as to whether many of these patients do not have a more or less chronic infection of the kidney from the beginning of the urinary symptoms. An infected kidney does not continuously pass organisms into the urine. An area of infection may be walled off so that the urine is free from pus and organisms except at intervals when the area opens up and discharges into the calyx or pelvis. This is known to have occurred in several instances; the urinalysis did not indicate any infection in the kidney, although at operation or necropsy considerable evidence of infection was shown. I believe that this is a frequent condition in prostatic cases. As soon as any treatment is begun, the infection increases because of the changes brought about in the kidney, and bacteria and pus appear in the urine. The change in the urinary apparatus is made by the withdrawal of the residual urine. When the urine is free from bacteria before treatment is begun, but shows pus and organisms a short time afterward, it is usually believed that the infection is due to contamination during treatment. This is undoubtedly true in some cases, but it would seem that the appearance of pus and organisms in the urine does not necessarily mean the treat-

ment has caused an infection. Just why the kidneys become infected, and the route by which the infection enters them, has been the subject of considerable discussions. Crabtree and Cabot believe that the blood-stream is by far the most frequent source of infection. They cite the case of a man under preparation for prostatectomy whose urine at the time of admittance to the hospital was found by culture to be free from infection. The catheter had been in place for several days during which time there were no symptoms and the cultures were sterile. On the eighth day the patient complained of burning in the urethra; two hours later he had a chill and a sharp rise in temperature. Blood cultures made two and a half hours after the onset of symptoms showed a pure growth of colon bacilli. No bacteria were found in the cultures from urine made at the same time, but cultures of the urine several hours later showed abundant colon bacilli. The functional test dropped twenty points in twenty-four hours. The patient presented all the evidence of pyelonephritis, but with constant urethral drainage for another week renal function returned to within five points of the former reading. At this time a prostatectomy was performed. A secondary hemorrhage occurred on the ninth day and the patient died. The necropsy showed that the kidneys were pale and had normal markings. There was no dilatation of the pelves. Crabtree and Cabot believe this case to have been one of pyelitis and pyelonephritis. The diagnosis of pyelone-phritis was based on the sudden drop in the kidney function, which they think was due to cloudy swelling probably involving the tubular portion of the kidney. They believe that in such cases the perivesical tissue becomes infected, but instead of lymphatic extension to the kid-ney, which is against all rules, the infection enters by way of the blood-stream.

In some of these cases infection ascending by way of the urinary passages is probably the source of the kidney infection. Ordinarily, infection does not occur in this manner, but when there is an inflam-matory thickening in the wall of the bladder and also in the lower end of the ureter (especially if there is obstruction in the urethra, produc-ing back pressure into the ureter), infection may readily extend to the kidney through the lumen of the ureter.

Infection might ascend by way of the lymphatics if all the lymphatics were blocked, but under ordinary conditions, with the lymph draining normally, infection at the lower end of the ureter would be passed to the lymphatic glands in front of the sacrum. It is more likely that the

perivesical infection finally reaches the kidney by extending into the lymphatics and then entering the blood-stream.

The effect of the infection on the function of the kidney depends on the part of the kidney involved. There may be chills, fever, and considerable pus in the urine, and yet the renal function may not be greatly reduced. On the other hand, with little evidence of infection —no rise in temperature, no organisms in the urine—the renal function may be very greatly reduced. If the infection attacks the cortical part of the kidney, as is usually the case when it is of coccus origin, there will be considerable evidence of it, but the renal function may appear normal. If the infection enters the region of the tubules, even though it causes only a swelling in this region, the phenolsulphonephthalein output is usually greatly diminished. This type of infection is, as a rule, produced by the colon bacillus. If the infection is mixed and due to colon bacilli and cocci as well, there will be much pus in the urine, marked evidence of infection, and also greatly reduced function.

Infection in the ureter is generally secondary to an infection in the wall of the bladder. The ureter is dilated, the coats are greatly thickened, and there are no peristaltic contractions. The dilatation of the ureter must be due to the increased pressure, and the hypertrophy to the effort to force the urine past the obstruction. The trauma which precedes infection in the bladder and ureter is produced by the overdistention. Cystitis is often due to trauma produced by the catheter.

In the study of these cases bacteriologic examinations have been made of the urine and blood and also of the prostate and the wound after operation. In nearly all such examinations the blood cultures were negative, possibly because of the fact that they were not made immediately following the chill. According to Bumpus, cultures often will not be obtained from the blood a few hours after the chill.

The bacteriologic examination of the urine in five consecutive cases in which complete data were obtained showed that before treatment of any kind had been instituted Staphylococcus albus could be demonstrated in the culture in four of them. In one the showing was very scanty. In the fifth case no growth had developed in the media at the end of the fourth day. While all these cultures were taken with great care, it is not possible to be absolutely certain they were free from contamination. The presence of the cocci in the urine could not be explained. None of the patients had any rise in temperature or showed other evidence of infection.

A second bacteriologic examination of the urine was made of three of the five patients four days after the preliminary treatment was begun. The other two did not require preoperative treatment. It is especially interesting to note that in all the cases, in addition to the staphylococci that were present at the first examination, there were colon bacilli in some or all of the media. In Cases 3 and 4, in which a primary prostatectomy had been performed, the urine gave a positive culture of colon bacilli in one case on the fourth day after the operation, and in the other on the fifth day, so that all five patients had colon bacillus infection four or five days after the beginning of treatment. The patient who had a primary prostatectomy showed some evidence of infection. On the fourth day he developed a temperature of 101.5 F. In two instances cultures were taken of the hypertrophied prostate as soon as it was removed. The culture from the patient who had not had any preliminary treatment was negative. The culture from the patient who had been catheterized for several weeks showed a positive growth of colon bacilli.

The five patients all made good recoveries without complications. They were discharged with wounds completely healed within five weeks after the prostatectomy. Only one patient had a temperature as high as 102 F., and this lasted but a few hours. Possibly the convalescence in these cases was better than is usual, yet at approximately the same time after the beginning of treatment cultures of the urine in each case showed colon bacilli and staphylococci. This would seem to suggest either that these patients had a natural or acquired resistance to these bacteria, or that the bacteria were not especially active. There was no suggestion at any time of insufficient elimination from the kidney. Since positive cultures were found in all these cases, does it not seem probable that they are common in this condition? Such cultures point out what will take place if for any reason the patient's resistance is greatly lowered or the activity of the organisms is increased.

Vaccines were not given in these 5 cases. Recently we have made a study of 21 prostatic cases to determine the effect of the use of Bacillus coli vaccines. Twelve of the cases were preoperative and nine postoperative. Each patient received Bacillus coli vaccine every four days, beginning with 50 million and increasing to 500 million, the maximum dose. A microscopic examination of the urine was made every week, and, with one exception, colon bacilli were found. However, none of the 21 patients has shown any evidence of severe infection, and it is

possible the use of the vaccine may have modified the infection consid-
erably in spite of the fact that the colon bacilli persisted in the urine.
Two of the 21 patients had chills. A blood culture made from one at
the beginning of the chill was sterile. Both had white blood counts
during the chill, showing only about 25,000 leukocytes. The phenolsul-
phonephthalein output dropped 10 to 15 per cent at the time of the
chill.

CONCLUSIONS

1. In prostatic cases a definite reaction occurs during the preopera-
tive treatment. In some cases this reaction may be due to infection
in the kidney.

2. Several days after the beginning of treatment or after the opera-
tion has been performed, in a very large majority of cases, the urine
shows a considerable number of colon bacilli. This cannot be due to
contamination in every instance, although we are unable to say whether
it comes from the kidney, the bladder, or the prostate itself.

3. The infection may be walled off in the kidney, and therefore no
organisms will show in the urine. Simultaneously with any form of
treatment the infection becomes active and the urine immediately shows
bacteria.

4. Colon bacillus vaccine may modify the infection, though it does
not decrease the number of colon bacilli in the urine.

CASE REPORTS

CASE 1 (A186131).—S. H., a farmer fifty-seven years of age, married
thirty years, 12 children. Urgency of urination, smarting, and burning
had existed for eight years and dribbling for three years. There had
never been complete retention, and a catheter had never been used.
The patient had lost 15 pounds in weight. There was bilateral enlarge-
ment (encapsulated) of the prostate, 3 on a scale of 4. The bladder
was distended. The right eye showed secondary optic atrophy; the left
eye was negative. A twelve-hour specimen of the urine, 600 c.c., had a
specific gravity of 1026, an acid reaction, and an occasional pus-cell, but
was otherwise negative. Combined phenolsulphonephthalein test: 260
c.c., 60 per cent in three hours. There were 8 ounces of residual urine.
The blood Wassermann test was negative. Blood urea (Van Slyke): 29
mg. of urea per 100 c.c. The preparation of the patient consisted of cath-
eterization twice a day for a few days and the use of a permanent cath-
eter for several weeks. There was considerable general decline when the
catheter was first used, but the subsequent improvement was marked.
The blood-pressure before treatment was 125, 83. The phenolsulphone-

phthalein return varied from 35 to 70 per cent in two hours. On the eighth and eighteenth days during the preparation a chill, followed by a rise in temperature, occurred. A suprapubic prostatectomy was performed, the capsule being sutured and the bladder completely closed. A urethral catheter was inserted for drainage. The temperature did not run above 100, there were no complications, and the patient was dismissed with his wound entirely healed on the eighteenth day.

Examination of the blood before any preparation was made showed 70.7 per cent polynuclears and 5400 leukocytes. At the time of the prostatectomy there were 74 per cent polynuclears and 13,200 leukocytes. Several days after the prostatectomy there were 86.7 per cent polynuclears, and 25,600 leukocytes.

Bacteriologic examination of the urine before any treatment revealed Staphylococcus albus and a large saprophytic coccus on all media. The anaërobic culture was not good. Bacteriologic examination of the urine after four days of repeated catheterization showed Bacillus coli, staphylococcus, and yeast-cells on a blood-agar culture. Bacillus coli and a staphylococcus were present on glucose agar. Bouillon gave a growth of Bacillus coli. Anaërobic cultures showed Bacillus coli and staphylococcus. Cultures of the urine some time after operation showed the pneumococcus on all media.

Bacteriologic examination of a glucose-agar culture of material taken from the gland at the time of prostatectomy showed the pneumococcus and Bacillus coli. Blood-agar, bouillon, and anaërobic culture gave growths of Bacillus coli and a gram-positive diplococcus, probably a pneumococcus.

CASE 2 (A184364).—G. H. L., a farmer, sixty-one years of age. This patient was an old alcoholic and had had frequency of urination for five years. One week previous to our examination he had acute retention. The catheter was used once and since then there had been incontinence. Weight normal. Heart action slightly irregular. Hemorrhoids. Rectal examination revealed a large benign prostate. The blood-pressure after treatment was 150, 88. Urinalysis: 400 c.c., specific gravity 1018, albumin, red blood-cells, and white blood-cells. Blood-urea: 21 mg. in 100 c.c. Phenolsulphonephthalein test: 45 to 50 per cent returned in seven to seventeen minutes. Because of the acute retention and much pain on passing the catheter, the preparation consisted in preliminary drainage of the bladder by suprapubic cystostomy. During the two weeks following this operation there was continuous improvement and at the end of that time a prostatectomy was performed. The temperature rose to 102 + soon after the operation, but returned to normal in three days, and remained so until the patient was discharged with his wound healed at the end of four weeks.

The blood examination made when the patient was first seen and before any treatment had been given showed 70.7 per cent polynuclears

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and 15,600 leukocytes. Six days after the drainage operation there were 67.7 per cent polynuclears and 8200 leukocytes; six days after the prostate was removed, 77.3 per cent polynuclears and 18,400 leukocytes.

Bacteriologic examination of the urine before treatment revealed Staphylococcus albus in bouillon, glucose-agar, and blood-agar cultures. Anaërobic glucose-agar culture was sterile for four days. Bacteriologic examination of the urine after suprapubic drainage revealed the staphylococcus, pneumococcus, and Bacillus coli in a bouillon culture. Blood agar showed the pneumococcus and Bacillus coli. Anaërobic agar showed the Bacillus coli and pneumococcus. Bacteriologic examination of the urine eight hours after prostatectomy showed the Bacillus coli and streptococcus in glucose-agar culture. Blood agar gave a growth of Bacillus coli and a diplococcus. Anaërobic culture showed the Bacillus coli. Blood-agar and bouillon cultures of the urine six days after prostatectomy showed the Bacillus coli and a streptococcus. Glucose agar gave a growth of Bacillus coli and pneumococcus.

Bacteriologic examination of a culture taken from the wound four days after suprapubic drainage showed a staphylococcus in bouillon. The anaërobic culture was sterile. Glucose agar and blood agar showed the Staphylococcus albus and Bacillus coli. A culture made from the wound at the time of the prostatectomy showed Bacillus coli and staphylococcus. Six days after the prostatectomy, cultures from the wound showed the staphylococcus and Bacillus coli on glucose agar and in anaërobic media.

CASE 3 (A4162).—M. D. S., a banker, fifty-six years of age; married twenty-eight years; two children. This patient had had urinary difficulty for six years, gradually growing worse. For three years he had had dribbling. He had never used a catheter. The physical examination was negative except that a hard and encapsulated enlargement of the prostate was palpated per rectum. The blood-pressure was 154, 98. Urinalysis: 400 c.c. in twenty-four hours; specific gravity 1021; slight amount of albumin and pus. The blood examination showed 83 per cent hemoglobin and 9400 leukocytes. There was 1 ounce of residual urine. Phenolsulphonephthalein test: 50 per cent returned in two hours. Blood urea: 33 mg. to 100 c.c. It did not seem necessary to institute any preliminary preparation. A prostatectomy was done without the drainage operation, as the amount of residual urine was small and the other examinations were satisfactory.

Examination of the blood on the day of the operation showed 66.7 per cent polynuclears and 8800 leukocytes. Four days after operation there were 84 per cent polynuclears and 11,600 leukocytes.

Bacteriologic examination of the urine before operation showed a scanty growth of staphylococci on all media. The blood-agar culture of the urine five days later (the patient's temperature had been 101.5 F. the evening before, the highest at any time during the convalescence)

showed Bacillus coli, staphylococcus, and pneumococcus. A bouillon culture gave a growth of pneumococcus and staphylococcus. Glucose agar showed Bacillus coli and staphylococcus. The anaërobic culture showed Bacillus coli and pneumococcus.

A culture made from the prostate soon after it was removed showed no growth.

The convalescence was uneventful and no evidence of infection was noted at any time. The wound was slow in healing, but this was evidently due to the condition in the prostatic urethra and not to the infection.

Case 4 (A187926).—J. L. G., a janitor, sixty-five years of age; married thirty-four years; three children. The urinary difficulty had begun three years previously with urgency of urination and dribbling. The patient had never been catheterized. The physical examination was negative except that on palpation per rectum the prostate seemed to be benign, but enlarged, firm, and hard. The blood-pressure was 150, 115, and 150, 90. Urinalysis: 600 c.c. in twelve hours; specific gravity 1030; otherwise negative. Phenolsulphonephthalein was returned in fifteen minutes, 60 per cent in two hours. There were 2½ ounces of residual urine. Blood urea: 37 mg. in 100 c.c. Examination of the blood showed 54 per cent polynuclears and 4800 leukocytes. As the patient's general condition was good, the amount of residual urine small, and the specific gravity and renal function normal, it was not considered necessary to institute preliminary treatment, and suprapubic prostatectomy was performed.

Examination of the blood on the day of the operation showed 86 per cent polynuclears and 10,600 leukocytes. Four days after the operation there were 80 per cent polynuclears and 10,500 leukocytes.

Bacteriologic examination of the urine before any catheterization and before the operation showed staphylococci in all cultures. Anaërobic and aërobic cultures in bouillon and glucose agar were sterile. Blood agar showed no hemolyzing streptococci. Four days after the operation a glucose-agar culture of the urine showed Bacillus coli and pneumococcus. Blood agar also gave a growth of Bacillus coli and pneumococcus. Anaërobic and aërobic cultures in bouillon showed Bacillus coli and pneumococcus.

Four days after the operation a culture from the wound showed Staphylococcus albus.

There was no rise in temperature or suggestion of infection at any time during the convalescence (the temperature was never more than a fraction above 99 F.), but on the sixth day a considerable number of colon bacilli and cocci were found in the urine. The wound healed in a little more than three weeks.

Case 5 (A150733).—J. M. P., a laborer, sixty-five years of age; married forty-four years; four children. The urinary difficulty con-

sisted in smarting on urination for the previous three years. Examination per rectum revealed a median enlargement of the prostate. The blood-pressure was 128, 86 and 135, 95. Urinalysis: 750 c.c. in twelve hours; specific gravity 1028; otherwise negative. There were two to three ounces of residual urine. Phenolsulphonephthalein test: A showing in ten minutes, 35 per cent in two hours; second test, a showing in fifty minutes, 50 per cent in two hours. Blood urea: 30 mg. in 100 c.c. and 42 mg. in 100 c.c. In spite of the good renal function, it seemed best to make a suprapubic drainage before removing the prostate, as the patient was not in a good general condition. No reaction followed the drainage of the bladder, and about three weeks later a suprapubic prostatectomy was performed. The temperature was 100 F. on the second and third days following the operation, but was not above normal at any other time during the convalescence, and the patient was discharged on the nineteenth day with his wound healed.

Examination of the blood at the time the operation for drainage was performed showed 85.3 per cent polynuclears and 22,400 leukocytes. Five days later there were 80.3 per cent polynuclears and 13,000 leukocytes. At the time of the prostatectomy there were 61.7 polynuclears and 18,000 leukocytes.

Bacteriologic examination of the urine at the time of the operation for drainage of the bladder showed pneumococcus on the blood-agar culture, but there was no growth on the other media. Before any treatment had been instituted, glucose-agar, bouillon, and anaërobic cultures were all sterile for four days. Four days after drainage of the bladder an agar culture showed staphylococcus, streptococcus, and Bacillus coli. A staphylococcus and a gram-negative saprophytic organism were found on anaërobic culture. Bouillon culture showed streptococcus and staphylococcus and a gram-negative bacillus. At the time of the prostatectomy, glucose-agar, blood-agar, anaërobic cultures, and bouillon showed Bacillus coli and pneumococcus. Glucose-agar, blood-agar, bouillon, and anaërobic cultures of the urine four days after prostatectomy showed pneumococcus and Bacillus coli.

A glucose-agar culture of material taken from the wound four days after the prostatectomy showed large gram-negative saprophytic bacilli, probably saprophytes.

In spite of the fact that many organisms were present in these cultures, the patient showed no evidence of infection at any time and made a prompt recovery.

THE ADVISABILITY OF PROSTATECTOMY IN THE PRESENCE OF CORD LESION*

E. S. JUDD AND W. F. BRAASCH

In the examination of the central nervous system of patients with urinary incontinence following prostatectomy, it is not uncommon to find definite evidence of cord lesions. On investigation it is usually discovered that the patient had complained of urinary difficulty even prior to the prostatic age, and that definite evidence of a central nervous system lesion had been overlooked. The urinary symptoms were evidently the result of disturbance in the central nervous system and were not caused by the enlargement of the prostate that may have been felt per rectum. Even when no such enlargement was palpated the surgeon may have felt justified in advising a prostatectomy because of the possibility of median lobe obstruction. It is now recognized that urinary obstruction may be due to many conditions other than those discovered by means of rectal palpation and the urethral sound. When any doubt remains, the etiologic factor can usually be ascertained by a careful examination of the nervous system and by cystoscopy.

The physical examination of a series of patients who had cord lesions and who complained of urinary disturbance showed that evidence of the lesion in the central nervous system is often apparent even on casual examination. Occasionally, however, the cord lesion is obscured and is discovered only after a careful search. Rectal examination of patients with advanced cord lesions and urinary difficulty shows that the prostate is apparently smaller than normal, the periprostatic tissues are often flabby, and any slight degree of prostatic enlargement that may be present seems to give on pressure as though there was no resistance in the tissues back of it. Occasionally, however, the urinary difficulty seems to be caused by a well-marked enlargement of the prostate and only on careful examination is definite evidence of cord lesion determined in

addition. The question then arises: Are we justified in performing prostatectomy in the presence of a cord lesion?

The decision as to the advisability of an operation will usually depend on the relative degree of the symptoms of obstruction due to the enlargement of the prostate and the extent of the nerve lesion. Although operation is usually contraindicated by incontinence, it may occasionally be advisable. If the incontinence is due to weakness of the external sphincter, prostatectomy is not advisable, but if the incontinence is due to overflow of retained urine, as is not infrequently the case in uncomplicated hypertrophy of the prostate, the operation may be justified. The tone and strength of the muscular coat of the bladder are best estimated by watching the change in the amount of residual urine and the force with which the stream is propelled through a catheter. If the tone is good, the urine is passed vigorously until the bladder is empty, without the use of the accessory abdominal muscles. If the muscular tone is failing, the stream flows quietly, its force being altered by any change in the abdominal muscles and by respiratory movements. It may require pressure with the hand to completely empty the bladder. Under these circumstances the organ does not contract uniformly, but often falls into folds leaving separate pouches filled with urine. In such cases overdistention may temporarily increase the impairment of tone. It is said that the persistent use of a catheter sooner or later results in complete distention, and that in two years' time the expelling power will not return. This may be true when the difficulty is due to a nerve lesion. On the other hand, if the obstruction is mechanical, a catheter may be used for many years without any impairment of the expelling power and the patient will completely empty his bladder after the obstruction has been removed. The overflow, often observed in the presence of prostatic enlargement, usually begins at night when the patient is relaxed, but may be brought on by sudden exertion.

Incontinence is not a common symptom of uncomplicated prostatic enlargement. If there is true incontinence, the bladder is always found empty since the urine passes out as quickly as it enters, but if the leakage of urine is due to overflow, the bladder is always completely filled and just a small amount escapes. Incontinence may be due to the fact that the enlargement of the prostate keeps both the external and internal bladder sphincters continuously relaxed. However, we have never found a total incontinence of urine due to enlargement of the prostate. In many cases of enlargement of the prostate we have seen a loss of func-

tion of the internal sphincter so that the bladder and prostatic urethra were one continuous cavity, but in all instances the sphincter external to this part of the urethra was normal and did not allow the urine to escape. This shows how important it is not to disturb the external sphincter in operating for enlargement of the prostate.

True incontinence is usually due to the lesion in the nervous system. With the exception of trauma, tabes dorsalis is the most common form. Bladder symptoms may be the very first indication of locomotor ataxia, and as the enlargement of the gland and tabes dorsalis occur at about the same age and time of life, it is easy to make a mistake in the diagnosis by attributing the urinary symptoms to the enlargement of the gland, when in reality they are due to the condition of the nervous system. In only a few selected cases of coexisting enlargement of the gland and tabes dorsalis should operative interference be undertaken. It is easily seen that if the condition is due to a lesion of the nervous system relief will not be obtained by operating, and in all probability many patients are better off with some mechanical obstruction due to the enlarged gland than they would be with the obstruction removed and with total incontinence of urine. All tabetics do not have involvement of the portion of the cord which controls the urinary mechanism, so that a person may have tabes dorsalis and also have good control of the bladder sphincter. Fortunately, the presence or absence of sphincter control can be demonstrated by a careful cystoscopic examination. If the cystoscopist finds that the sphincter is functionating and that the symptoms are due to the enlargement of the prostate, it is proper to remove the gland since good functional results are obtained, even though tabes is present. This is a very important consideration. We have frequently observed patients with a loss of sphincter control who said that under these circumstances existence was almost unbearable. When there is not a total incontinence but extreme urgency of urination, the condition is nearly as distressing because it necessitates the wearing of a urinal in order to keep the clothing dry. The functional result may be one of the chief considerations in all prostatic and bladder cases. It should be very carefully considered before any operation is attempted, especially if the patient is suffering from tabes dorsalis. When the clinical evidence of advanced cord lesion is well marked, there being ataxia, cerebral symptoms, or incontinence resulting from weakness of the external sphincter, operation would, of course, be contraindicated. If, however, the cord lesion is determined only after a careful, painstaking examination, it may be

necessary to make a careful cystoscopic examination in order to determine the major factor in the urinary obstruction.

The data obtained by cystoscopic examination of patients suffering from lesions of the central nervous system are of much importance in the differential diagnosis. In instances in which the urinary obstruction is caused by such cord lesions, typical changes in the appearance of the interior of the bladder and the sphincters may be observed by cystoscopic and urethroscopic examination. The changes usually regarded as typical and which are most prominent are the characteristic trabeculation and relaxation of the sphincters. The trabeculæ are not as coarse as is usual when there is mechanical obstruction. They appear more ridge-like and frequently extend continuously over a large part of the circumference of the bladder. Caulk and Greditzer maintain that the condition of the sphincters is of great importance in the diagnosis. In a recent article they described the relaxed condition of the internal sphincter and prostatic urethra. This atonic state of the prostatic urethra is usually accompanied by a reduction in sensation.

Young, in an article in which he described a punch operation for removing median bars, also says he has operated on several tabetics in this way with fairly satisfactory results.

In reviewing the surgical records of the Clinic, it was found that a prostatectomy has been done in nine patients in whom there was definite evidence of a cord lesion on clinical examination. There were also a number of patients with well-marked hypertrophy of the prostate who gave a definite history of early lues. Several of these had a positive Wassermann reaction but no clinical evidence of a cord lesion and were consequently not included in this series. A study of the clinical data and a review of the postoperative results obtained are of considerable interest.

As regards the subjective symptoms other than the urinary difficulty there was an absence of definite data and more confusion than is usual in cases of cord lesions. The examination of the nervous system of most of the patients operated on showed that the upper portion of the cord was more involved than the lower. The absence of incontinence after the operation in all cases would seem to corroborate the accuracy of the preoperative examination of the nervous system. Only three patients of the nine gave a positive history of having had an initial lesion. Two gave a history of having had pain referred to the extremities, and this only to a moderate degree. A slight degree of ataxia was noted in two

patients. Although in six cases the onset of symptoms had occurred more than ten years previous to our examination, in only one had it been noted before the prostatic age. The initial symptom was usually frequency of urination, difficulty becoming predominant later. The catheter was used entirely in five cases and partially in the remaining five. A slight degree of incontinence was complained of in two cases. In both of these, however, there was a large amount of residual urine and the incontinence might be explained in part as being an overflow.

Examination of the nervous system revealed the fact that the different reactions varied from the normal to a moderate degree. The patellar reflex was entirely absent in two cases and markedly exaggerated in two. The Argyll-Robertson pupil was present in four cases, a definite Romberg in three, and a moderate ataxia in two. The Wassermann reaction was positive in two cases and negative in five. The amount of residual urine varied from one to fourteen ounces in the five cases in which the catheter had been partially used. The functional tests (phenolsulphonephthalein) in all cases were more than 40 per cent at the time of the operation.

On cystoscopic examination, as might be expected, the evidence of cord lesion was overshadowed by the changes resulting from mechanical urinary obstruction. The internal sphincter was relaxed in one case, but the external sphincter was not relaxed in any. As is usual in the presence of a cord lesion, cystitis was present only in a moderate degree. Stone in the bladder was a complication in one case. The degree of trabeculation was marked in only five cases, a fact suggestive of cord lesion. It would seem that when the gland is enlarged it might be difficult to determine by cystoscopic examination whether or not the urinary sphincters are relaxed. However, the knowledge of the exact degree of relaxation may not be necessary to determine the advisability of operation, since the character of the trabeculations and the appearance of the bladder-wall together with the presence or absence of incontinence and the clinical findings will usually offer sufficient data.

During this same period a large number of patients were examined who had well-marked clinical evidence of cord lesions, and more or less residual urine. On cystoscopic examination they also showed definite evidence of cord lesion. Some of these patients had a moderate degree of hypertrophy of the prostate and the advisability of prostatectomy might have been considered. However, the general condition, the well-advanced degree of the cord lesion as evidenced by the clinical symp-

toms, the dilated atonic bladder, and the relaxed condition of the sphincters contraindicated operation.

In the majority of patients in advanced stages of tabes, however, even though retention is present, the prostate appears smaller than normal upon palpation per rectum, and there is an abnormal relaxation of the tissues about the prostatic area. Therefore the advisability of operation would depend largely on the comparative degree of cord involvement. When it is evident that the sphincter itself is not relaxed, that there is sufficient hypertrophy of the prostate to account for the urinary obstruction, and that the general condition is favorable, prostatectomy may be attempted.

In this connection we may refer also to the so-called atonic bladder. This condition, which has been fully described by Walker, is characterized by a dilated bladder and residual urine without any definite evidence of disease in the nervous system or any clinical cause to account for the obstruction. Another cause for urinary obstruction is occasionally observed in cases in which the prostatic hypertrophy obstructs the urethra without causing an enlargement that can be palpated on rectal examination or observed by cystoscopic examination. Urethroscopic examination alone will reveal a peculiar overlapping of the lateral prostatic lobes which may cause marked urinary obstruction.

Answers to letters of inquiry relative to the postoperative results in these nine cases have been received from eight of the patients. One patient died eighteen months after the operation. The other eight are reported in good condition and have no urinary difficulty except in one instance. The latter was the last patient in the series to be operated on, the operation having been performed some six months before. He still complains of considerable frequency of urination and recently of a slight degree of incontinence. The results indicate that prostatic hypertrophy was the predominant factor in the obstruction. Three of the patients underwent a thorough course of antisyphilis treatment, including injections of salvarsan. This treatment seemed advisable, following the operation, as a preventive measure.

Case Reports

Case 52394.—A patient, seventy-two years of age. No history of lues or previous diseases. He had had trouble for fourteen years, beginning with increased difficulty in urination. A catheter had been used part of the time recently; some pain in the suprapubic region, perineum, and

bladder. A general examination of the nervous system did not reveal a cord lesion. Cystoscopic examination showed 14 ounces of residual urine and a typical picture of cord bladder. Cystitis (1 on a scale of 4). Trabeculations were typical of cord lesion. Suprapubic prostatectomy was performed July 28, 1911. The patient returned about a year later for the removal of stones. The use of a catheter was necessary occasionally, although the functional result was fair and apparently much benefit was derived from the operation.

CASE 62477.—A patient, fifty-one years of age, who gave a history of having had lues. He came for treatment for urinary difficulty which had started two years previously. Bladder symptoms were marked; a catheter had been used continuously for three weeks, and there was considerable sacral pain. Examination of the nervous system showed that there was slight urinary incontinence. Right patellar reflex absent, left exaggerated. Pupillary reflexes slow. Romberg absent. One ounce of residual urine; prostate enlarged, 2; a moderate degree of cystitis. The cystoscopic picture was not wholly characteristic. Blood Wassermann test positive. A suprapubic prostatectomy was performed January 10, 1912, and a good functional result was obtained. One month after the operation it became necessary to pass a sound a few times.

CASE 74852.—A patient, seventy years of age, with a history of five years of urinary difficulty. Three years previously he had had an attack of sudden retention; he complained of pain in the back, legs, and suprapubic region. Examination of the nervous system showed an absence of patellar reflexes. Ataxia was marked. Examination of the bladder showed enlargement of the prostate, 3. The urine was all residual. There was marked typical bladder trabeculation. Suprapubic prostatectomy October 14, 1912. Following the operation he had a little difficulty in urinating. He died in March, eighteen months later.

CASE 82406.—A patient, sixty-five years of age. Three weeks before coming for examination he had had a severe hemorrhage from the bladder. During the past two years he had had slight hematuria and had used a catheter almost continuously for several weeks. Examination of the nervous system showed most of the characteristic symptoms of tabes. Examination of the bladder showed that all of the urine was residual; cystitis, 2, stones in the bladder and marked trabeculation of the typical cord lesion type. Blood Wassermann test positive. Suprapubic prostatectomy was performed April 30, 1913. A large tabetic bladder with a thick wall and poor contracting power was found. The result in this case was very satisfactory although stones formed in the bladder and were removed elsewhere a year or more later.

CASE 89916.—A patient, sixty-two years of age, who gave a history of having had lues. He came because of urinary difficulty which he had had for six months. A catheter had been used continuously for two

months. He had an Argyll-Robertson pupil and Romberg. Cysto-
scopic examination showed a typical cord bladder, and in addition, con-
siderable cystitis. The trabeculation was characteristic. Suprapubic
prostatectomy April 4, 1916. At the present time (May, 1917) this
patient reports that he has gained 20 pounds and has no urinary diffi-
culty or hematuria.

CASE 107150.—A patient, fifty-four years of age, with a history of
having had an injury to the spine thirty-three years previously. Since
that time there had been some difficulty in urinating, though most of the
trouble had come in the last three years. A catheter had been used a
part of the time. Examination of the nervous system showed an absence
of the patellar reflexes. Bladder examination revealed 10 ounces of
residual urine. The internal bladder sphincter was relaxed and there
was considerable cystitis and very marked trabeculation of the cord
lesion type. Suprapubic prostatectomy June 17, 1914. A very large,
thick-walled bladder was found, and after the operation there was a
moderate degree of incontinence which persisted for several months.
This gradually lessened and at the present time the functional result is
very good, the patient reporting that he has no trouble of any kind.

CASE 114446.—A patient, seventy-four years of age. He had had
some sort of an injection over the bladder region fifty-three years previ-
ously. He had had his frequency for about twenty years and had used a
catheter almost continuously for three years. Examination of the ner-
vous system showed slight urinary incontinence; patellar reflexes ab-
sent; Romberg present; ataxia. Bladder examination showed nearly
all the urine to be residual; cystitis 2, with the characteristic trabecula-
tions and relaxation of the bladder seen in these cord cases. A supra-
pubic prostatectomy was performed September 24, 1914, with a good
result except that the frequency persists and urination occurs every few
hours.

CASE 177201.—A patient, sixty-eight years of age, who had had
urinary frequency for fifteen years and had used a catheter off and on for
two years. He complained of some pain in his legs. Examination of
the nervous system showed that the patellar reflexes were diminished
and the pupils responded slowly; Romberg present. A bladder ex-
amination showed 6 ounces of residual urine; cystitis 2. A suprapubic
prostatectomy, performed November 21, 1916, had a satisfactory result
as far as function is concerned, but the cystitis has persisted, and occa-
sionally there is some difficulty of urination and the passage of a little
blood.

CASE 178746.—A patient, sixty-seven years of age, with a history of
having had lues. He came because of difficulty of urination which
began ten years before. He had used a catheter off and on for nine
months. On examining his nervous system it was found that the pupil-

lary reflexes were unequal and sluggish.   Romberg was present.   Bladder examination showed eight ounces of residual urine with cystitis and typical trabeculations.   A suprapubic prostatectomy was performed December 20, 1916, and was an entire success.   The patient still complains of feeling awkward below the knees.

REFERENCES

1. Caulk, J. R., and Greditzer, H. G.: Observations on the bladder in diseases of the central nervous system—an analytical study of 117 cases, Am. Jour. Syph., 1917, i, 42–57.
2. Young, H. H.: A new procedure (punch operation) for small prostatic bars and contracture of the prostatic orifice, Jour. Am. Med. Assn., 1913. lx, 253–257.
3. Walker, J. W. T.: Atony of the bladder without obstruction or signs of organic nervous diseases, Ann. Surg., 1910, lii, 577–596.

SURGICAL TREATMENT OF THE PROSTATE*

E. S. JUDD

The history of the surgery of the prostate does not date back as far as that of the surgery of many other organs. The results following surgery in the early days were often unsatisfactory in patients who survived the operation. For such reasons the development of this branch of surgery has not been especially rapid, and various types of operations and methods of operating have been advocated and tried.

A satisfactory etiology has not been offered to explain the development of the fibro-adenomatous hypertrophy which is by far the most common pathologic condition. I shall discuss in this paper some of the points dealing with the surgery of this type of benign enlargement occurring in the prostate. Fibro-adenomatous hypertrophy probably describes the pathologic lesion better than any other term, although I am convinced that the enlargement in the prostate bears the same relation to that gland that many other neoplasms bear to the glands in which they arise. The term prostatectomy is incorrect in the sense of removing the gland. I have demonstrated many times that the tissue we leave and which forms the so-called capsule is prostatic tissue. The enlargement which is removed in performing the operation is enucleated from the gland in much the same manner that an adenoma is removed from the thyroid, or a fibroid tumor from the uterus. While the lesion apparently begins in the so-called median or lateral lobes, I believe that most often the enlargement itself occurs as a single lesion and is not divided into lobes. At least it is certain that in the transvesical enucleation of the enlargement it will usually be removed in one piece.

A considerable part of the early surgery of the prostate was done in England and France, though I believe there can be no question that it has advanced farther in this country than elsewhere. The valuable work done in several of our clinics on the preliminary preparation of the

patients for operation, the development of accurate technic, and the proper after-care has greatly reduced the mortality and established very satisfactory results.

The cautery operation, as advocated by Bottini and others, was at one time employed considerably, undoubtedly because of the high mortality following other methods of operating. This is probably seldom if ever used now.

The punch operation as devised by Young undoubtedly is very useful in selected cases, especially in the type of small, hard, fibrous enlargement which is frequently difficult to remove otherwise. The punch operation is not a simple procedure: it requires considerable skill to perform it accurately. Open operations will be required afterward on some of the patients who have been operated on by this method.

In the development of operations for the removal of the enlargement from the prostate, much controversy arose between advocates of the perineal and the suprapubic or transvesical method of operating. While most surgeons are now performing the suprapubic operation because of the assured functional result, nevertheless many are employing the perineal method on account of the claim of lower mortality. The transvesical operation is technically easier to perform and is not liable to be followed by complications such as injury to the rectum and permanent fistulas which occasionally follow the perineal method. Furthermore, the transvesical is a much more accurate and definite surgical procedure, since it is possible to inspect the inside of the bladder and perform each step of the operation under the guidance of the eye. In operating through the perineum, the condition of the bladder and the extent of the median part of the enlargement must be determined by previous cystoscopic examination or by the finger introduced into the bladder at the time of operation. If the perineal operation is done, a large incision should be made so that any injury to the control-muscle fibers may be corrected. If the perineal operation has any advantage over the transvesical, it is in the lessened liability to infection. The tissues in the perineum are less susceptible to infection than are those in the prevesical space. Infection is such an important consideration in these cases that it is necessary to resort to the perineal operation with some chance of an unsatisfactory functional result or else to develop a definite transvesical technic, which, with the aid of other improvements, will control the factor of infection. Infection in itself may not be especially evident locally and may not seem severe, though it apparently
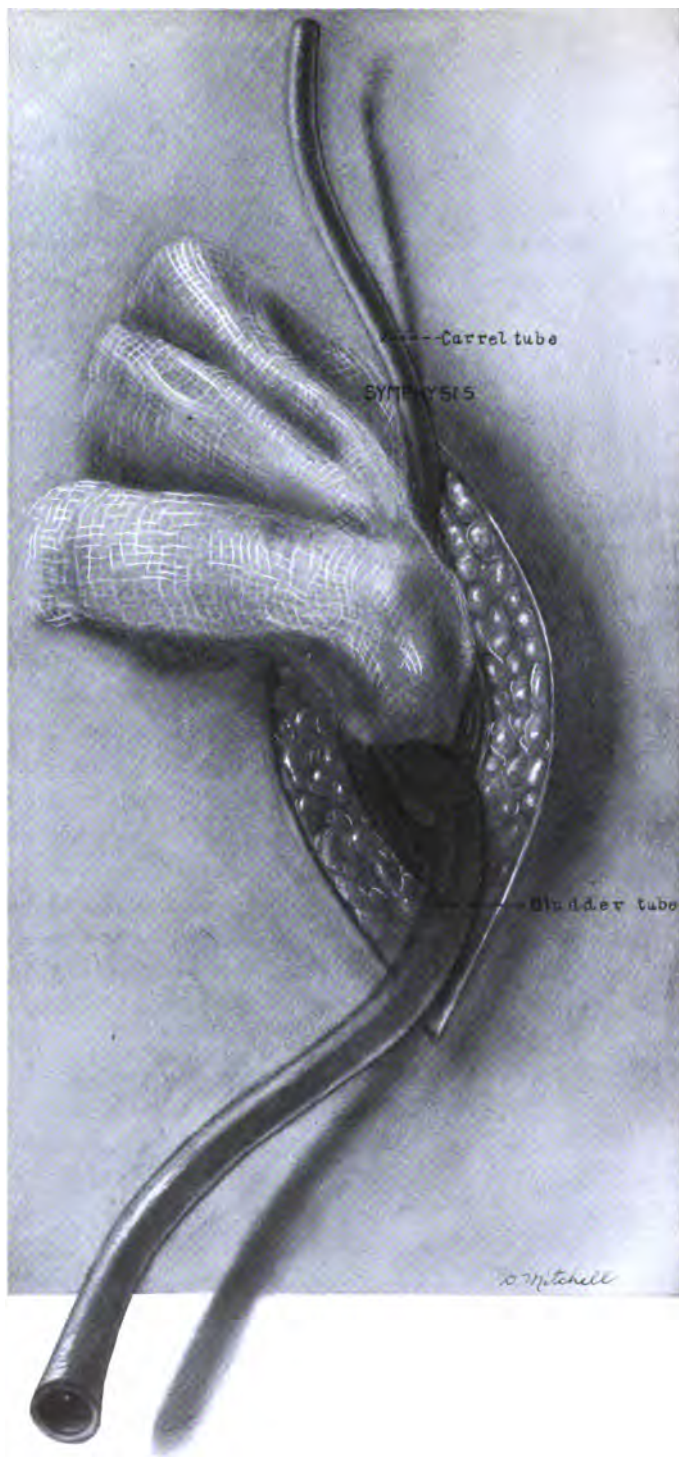
Fig. 90.—Large catheter in the bladder at the upper angle of the incision   Carrel tube with gauze in the pre-
vesical space.

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has a characteristic effect and sometimes a most serious outcome. To illustrate what is meant by this characteristic effect, I should like to compare this condition with other surgical procedures, for example:

A patient at the prostatic age, having cancer of the stomach or of the colon, is to be operated on for one of these conditions. The operation would probably require an hour's time; it might mean the soiling and infection in the abdominal tissues, and yet a very large percentage of such patients recover after this more serious operation. If, however, the same patient should have retention of urine during his convalescence so that catheterization were necessary, recovery would be greatly retarded, and in all probability if death ensued it would be owing to this disturbance, which necropsy would show to be due to infection in the genito-urinary tract, rather than to the effects of the operation on the stomach or colon. It would seem that the patient with prostatic trouble coming for treatment already has some infection or at least permanent injury of his kidneys, and that the elimination of certain toxins through the impaired kidneys may result very seriously. The mortality in prostatic cases is owing largely to uremia, brought about by an infection which throws the elimination of toxins to already damaged kidneys.

The degree of infection in the perineal or prevesical tissues may not seem great, and yet the general effect is pronounced. A two-step operation has been advocated by some surgeons because of the importance of avoiding infection. I do not believe this is often necessary or advisable. It is most important to carry out preliminary preparation in a large percentage of the cases, a measure which has done more for the surgery of the prostate than any other one factor. Preparation consists in ridding the patient of residual urine, cleaning up the infection, and increasing resistance as much as is possible. The withdrawal of residual urine and the preparation of the bladder by the use of the urethral catheter is preferable to preliminary drainage of the bladder through the prevesical space. In some cases it is impossible to pass a catheter, and in others large stones in the bladder may complicate the condition so that it may occasionally be necessary to perform the operation in two steps. Serious conditions may arise and seemingly unfortunate results follow urethral catheterization, though I feel certain that there will be much more frequent and more serious trouble following the drainage through a suprapubic incision. After the bladder has been opened and drained, and a sinus has persisted for some time, it is difficult to do an accurate operation through the opening without greatly en-

'17—17

larging it, and if the opening is enlarged the other tissues are immediately exposed to infection. If the gland is large, it may require considerable extension of the incision in order to remove it. If a drainage operation has been performed previously, the prevesical tissues will be firm and resistant and it may be difficult to reach the lower part of the enlargement. This difficulty may be partly overcome by introducing the finger or some kind of an elevator into the rectum, thereby lifting the gland up into the bladder. However, I believe this should be avoided whenever possible because it may invite infection and necessitate a much deeper anesthesia than is otherwise required in such cases. It is seldom necessary to employ this procedure in doing the one-stage operation, as the gland will be readily elevated as soon as the enucleation is begun. We have never seen injury to the rectum in performing the suprapubic operation.

The nature of the infection is not easily determined. The colon bacillus certainly plays a very important part. This bacillus may be derived from the urine of practically every prostatic patient. If it is not present on the first examination, it is certain to become evident after any form of treatment has been instituted. The urine may be free from organisms on the first examination and apparently it makes no difference whether the treatment is begun by interval catheterizations, in-dwelling catheter, preliminary cystostomy, or a primary prostatectomy. Within a very few days after any one of these procedures colon bacilli will be found in the urine. It would seem as though contamination might account for this at times, though it would scarcely be responsible in every instance. Whether this infection has its origin in the kidney, bladder, or prostate itself, is difficult to determine. Some investigators believe that it is primary in the tissues about the prostate, and that the organisms pass from these tissues into the lymphatics, then into the bloodstream, and are eliminated through the kidneys (Crabtree and Cabot). These investigators found colon bacilli in the blood two hours after a chill in a patient who was being prepared by an in-dwelling catheter. There were no organisms in the urine at this time though they appeared several hours afterward. Crabtree and Cabot interpreted this to mean that the organisms were passed from the prostatic tissues into the bloodstream and thence to the kidneys. In our own investigations we have found colon bacilli in the urine in practically all cases, but so far we have been unable to get a positive blood culture. We have taken cultures from the blood at all stages of the preliminary, operative and

postoperative periods, and at definite intervals following chills, and in each instance the culture was negative. While we are inclined to believe that these infections are frequently transmitted by the blood-stream, we have no definite evidence in our cases to support this theory. In our necropsy studies of operative and non-operative cases, we have
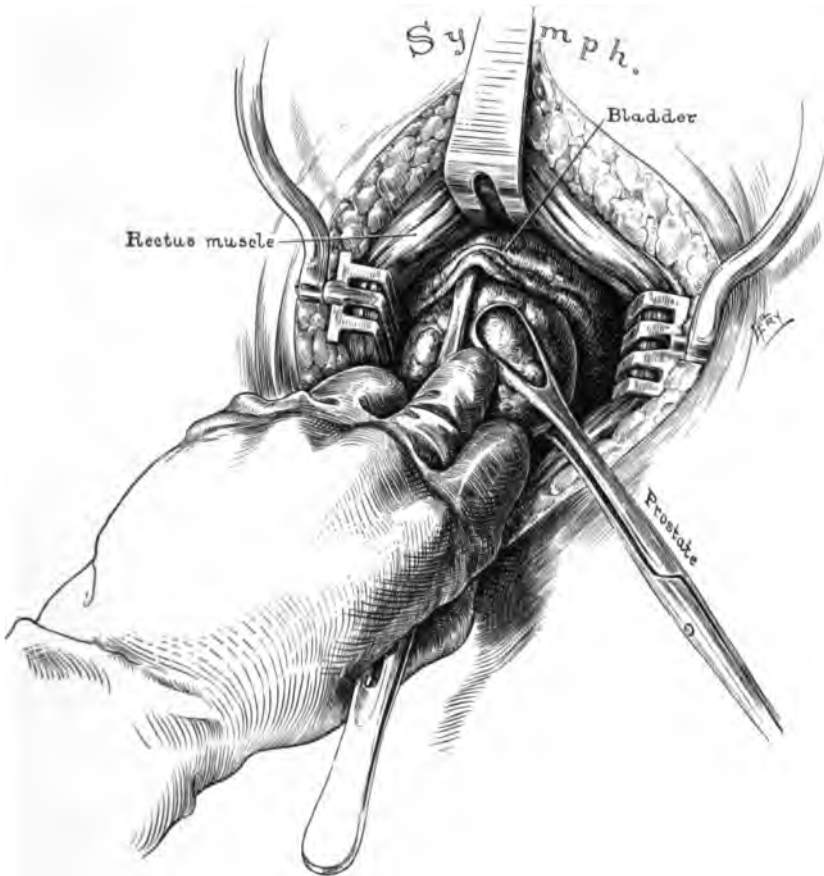
Fig. 91.—Separating the bladder mucosa from the enlarged prostate with dissecting forceps. Prostate being lifted into the field with a clamp.

learned that often the most severe infection is found in the tissues of the kidney and, furthermore, the kidney may be practically the only tissue infected. This is evidence which makes us believe that the kidney may sometimes be the primary seat of the infection instead of being secondary to some focus in the prostate or bladder.

In addition to the local preparation by means of the catheter we

believe positively that the patient's general resistance to infection has been increased by the use of vaccine. It is our custom to give stock

Fig. 92.—Enucleating with the finger an enlarged prostate adherent posteriorly.

colon vaccine, and we believe that it may not only help the patient to a comfortable convalescence free from temperature and chills, but that it may also be a factor in lessening complications and in reducing mor-

tality.   The patients are given vaccines every three days during their preoperative and postoperative treatment.   The dosage starts with 50 million bacilli and is increased in the course of nine days to 500 million, the maximum dose.   All patients are required to have three preoperative inoculations; the average number receive about seven.   In comparing the records of 23 vaccinated patients with 23 non-vaccinated patients, it was found that those vaccinated remained in the hospital an average of two and one-half days less and were discharged a half week earlier.   The most striking comparison, however, was the fact that there were eleven complications in the non-vaccinated patients to three in the vaccinated.*

Because of the general condition and the age of patients, the operation has often been performed as quickly as possible.   While it seems right that time should be something of a factor in the operation, nevertheless, a definite surgical technic should not be sacrificed in order to complete the procedure quickly.   A little more time would be well spent to make sure that the surrounding tissues are not soiled unnecessarily; that the bleeding is entirely controlled, and that the sutures are accurately placed in the tissues so that the urine will drain through the tube without infecting the prevesical space.   The technic of the operation is more important than the time consumed.   This is also an argument in favor of the transvesical method, as it is possible thereby to make the operation a more definite and accurate surgical procedure than by any other.

TABLE 1.—DATA FROM HISTORIES OF 46 PROSTATECTOMIZED PATIENTS
(JANUARY 1, 1917, TO SEPTEMBER 1, 1917)

	VACCINE 23 PATIENTS	NO VACCINE 23 PATIENTS
Cases of epididymitis......................	2	5
Cases of pyelonephritis....................	1	5
Cases of phlebitis.........................	0	1
Weeks of preoperative treatment............	5.5	3
Average number of doses of vaccine (preoperative)...................................	7	0
Weeks of postoperative treatment...........	4.5	5
Days in the hospital.......................	8	10.5
Average age.'.............................	66	62

We have employed local anesthesia in a few instances, and spinal anesthesia in a considerable number, without finding either an advantage.   General etherization has been most satisfactory.   The anesthesia is not deep and lasts only for a short time.   Pulmonary complications

* Administration of the vaccine has been done in our clinic by Dr. H. C. Bumpus.

very rarely occur in these patients. In addition to the ether, 0.5 per cent of novocain is injected into the prostatic capsule as soon as the bladder is opened. This seems helpful in several ways: (1) It almost entirely controls the oozing during the operation, so there is almost no loss of blood and the field is dry. (2) It helps to free the enlargement from the capsule and in this manner aids in the enucleation. (3) It produces an anoci-association and thus helps to avoid shock.

Inaccuracy of technic has been partly owing to the inaccessibility of the region, and we have endeavored to overcome this inaccessibility by improving the exposure. A self-retaining retractor is used which fits into the incision in the bladder and opens it, thereby enabling us to see the base and prostatic region. With the retractor in place, after the tumor has been enucleated, it is possible to see any bleeding vessels and catch them with plain catgut sutures. Most of the oozing comes from the torn bladder mucosa, although at times a fair-sized spurting vessel may be seen down in the prostatic capsule. Several interrupted sutures placed to include a little of the bladder mucosa and considerable of the prostatic capsule controls all the bleeding in most cases. In a few instances only will it be necessary to pack the capsule with gauze, though this should be done in case the bleeding is not well controlled. While this bleeding will always stop of its own accord, it seems to me that it is essential to have absolute control of it. The loss of a small amount of blood in itself is not so important, but it may reduce the general resistance to infection which it is so essential to maintain. If the bleeding is completely controlled, if the bladder is not infected, and if the patient is known to bear the urethral catheter well, the bladder may be completely closed and drainage instituted through a catheter in the urethra. The advantage of completely closing the bladder is that it reduces the possibility of prevesical infection. If there is any uncertainty as to the control of the bleeding or the condition of the bladder, a drainage-tube should be left in the suprapubic wound. If the suprapubic drainage-tube is employed, the bladder should be accurately closed about it, so that all the urine will drain through the tube. The disadvantage of the gauze pack in the capsule is that it allows urine to drain into the prevesical tissues.

In addition to the drainage-tube in the bladder, we have recently used Dakin's solution after the Carrel technic in the prevesical space for a few days following the operation. Our supposition is that no infection exists at the time of the operation, and by using this solution we

Fig. 93.—Deep enucleation with forceps.   Clamp pulling the prostate into view.

may be able to produce in this space media in which organisms will not survive. Whether this has been of any distinct value we are unable to say, but it certainly has done no harm and unquestionably we are now seeing less of this sort of infection than formerly.

The principal point in the after-care is to abandon treatment as far as possible and still keep the patients comfortable. It is necessary to
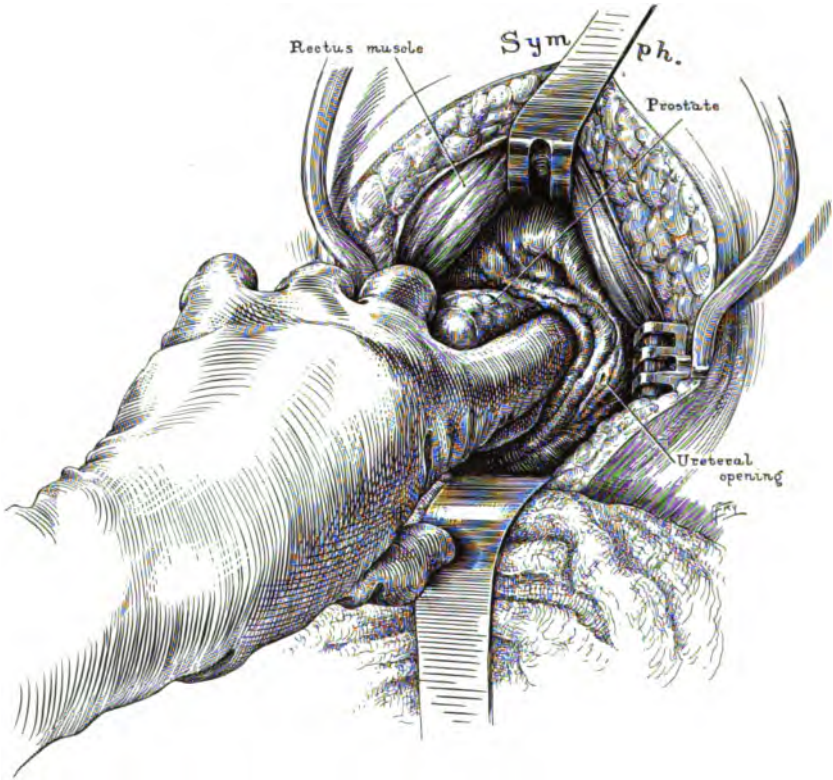
Fig. 94.—Separating the gland from the prostatic urethra.

keep the catheter draining; nevertheless, I think it is important to avoid irrigating the bladder. After the first few days, irrigation does no harm, but if employed from the start, it tends to prolong the oozing.

The following is a review of the patients operated on by us between January 1, 1917, and August 24, 1917:

TABLE 2

Patients...	84
Adenomatous hypertrophy and prostatitis....................	78
Carcinoma of the prostate.................................	4
Drainage preliminary to prostatectomy......................	10
(Nine under cocain and one under ether.)	
Two-stage operation.......................................	8
(The length of time between drainage and prostatectomy varied from two weeks to two years and two months.)	
Perineal prostatectomy....................................	1
Primary suprapubic cystostomy for prostatectomy.............	73
Deaths following preliminary drainage.......................	2
(One patient was uremic at the time of operation.)	
Deaths following drainage and prostatectomy.................	1
(Drained three months previously; capsule not injected or sutured; patient transfused with no benefit.)	
Prostatectomy with removal of stone........................	5
(Uneventful convalescence; bladder drainage in all.)	
Prostatectomy (diverticulum of the bladder).................	4
Diverticulum and prostate removed simultaneously............	2
Diverticulum not removed at the time of prostatectomy or subsequently...	2
Prostatectomy for carcinoma...............................	4
Suprapubic route...	3
Perineal route...	1
(Patients with carcinoma received from 200 to 1200 mg. hours of radium following operation.)	
Capsule injected but not sutured...........................	6
Capsule injected and sutured..............................	69
Capsule packed with gauze.................................	6
Bladder closed completely.................................	6
Bladder drained by a suprapubic tube.......................	81
Prevesical Carrel tube and gauze sponge.....................	69

Secondary hemorrhage following prostatectomy in two cases (eleventh and fifteenth day). In each case the capsule had been injected and sutured and a bladder tube inserted for drainage. Both were primary operations; both patients recovered.

CONCLUSIONS

1. The transvesical operation for the removal of enlargements of the prostate seems to be the most accurate, technically.

2. With great care to avoid infection, the operation can be done as safely as, if not more safely than, the perineal.

3. When possible, the preliminary treatment should be carried on by means of a urethral catheter, as it permits a better operation afterward. In some instances it may be necessary to do the operation in two stages.

4. Spending a little more time with the patient under a general anesthetic will permit a less spectacular but a much more satisfactory operation and the results will be good.

REFERENCES

Young, H. H.: A new procedure (punch operation) for small prostatic bars and contracture of the prostatic orifice, Jour. Am. Med. Assn., 1913, lx, 253–257.

Crabtree, E. H., and Cabot, H.: Colon bacillus pyelonephritis; its nature and possible prevention, Jour. Am. Med. Assn., 1917, lxviii, 589–591.

THE PRINCIPLES OF THE PATHOLOGY OF THE PROSTATE*

WM. CARPENTER MacCARTY

The pathology of the prostate, like that of any other organ, is dependent on certain biologic reactions of cells to antagonistic conditions of their environment.[1]

PRIMARY CYTOPLASIA

----Textocytes
----Textoblasts

SECONDARY CYTOPLASIA

----Textoblasts

TERTIARY CYTOPLASIA

----Textoblasts
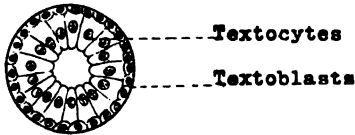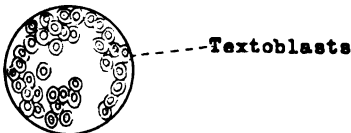
Fig. 95.—Diagrammatic representation of the three reactions which take place in the glandular epithelium (adenotex) in the prostate.

The problem, in considering the subject, resolves itself into answering the following questions: (1) What are the antagonistic conditions which involve the prostate? (2) What cells form the organ? (3) How do these cells react to the activity of antagonists? (4) How do the mechanical conditions of the organ affect its function and that of other organs? and (5) What simple terminology may be employed to express the reactions in an intelligent, descriptive communication of ideas between individuals who have to deal with the subject?

Although there are many possible antagonists to normal prostatic activity, ranging from direct trauma to most if not all the existing pathologic organisms, only relatively few have been described in connection with this organ. These, briefly enumerated, are Micrococcus gonorrhœæ, Staphylococcus, Streptococcus, Bacillus coli, Bacillus tuber-

culosis, and Treponema pallida. Descriptions of the peculiarities of reactions produced by each of these would be extremely academic because practically every text-book describes them in true classic form.

The biologic effects of these and other antagonists resolve themselves into the following definite reactions of all cells when in conflict with unfavorable environment:

1. Cytolysis (dissolution), which may be morphologically divided
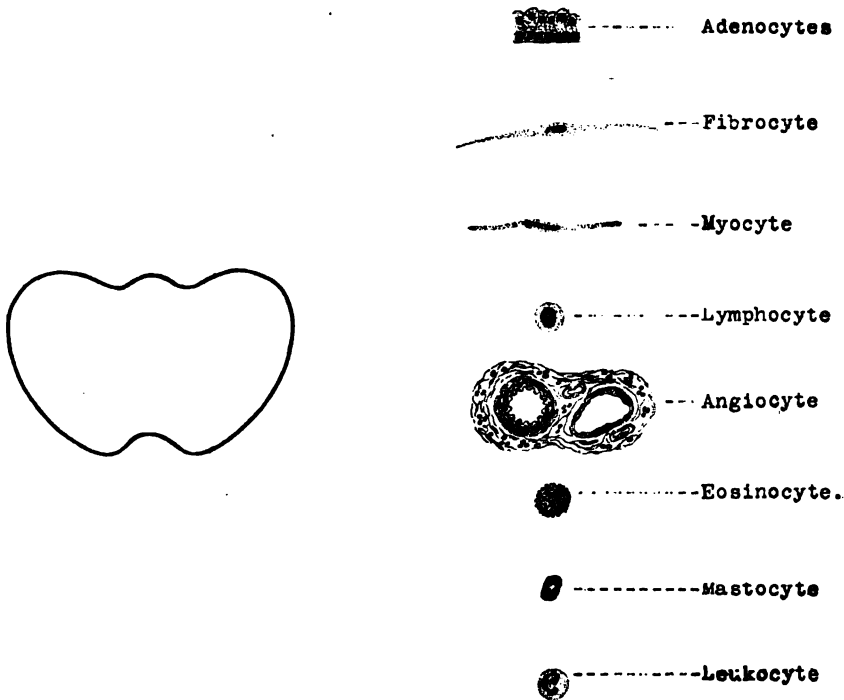
Fig. 96.—Diagrammatic representation of the tissues and cells of the prostate.

into the following three degrees: (*a*) Destruction of the cellular wall; (*b*) destruction of the cellular wall and the nuclear wall; and (*c*) the destruction of the whole cell.

2. Atrophy (reduction of size), which also presents three degrees of reaction, that is (*a*) Reduction of the cytoplasm; (*b*) reduction of the cytoplasm and nuclear plasm; and (*c*) the reduction of the whole cell.

3. Hypertrophy (increase in size), which occurs in the following three degrees: (*a*) Increase of the size of the cytoplasm; (*b*) increase of the

size of the cytoplasm and the nuclear plasm; and (c) increase in the size of the whole cell.

4. Neoplasia (cellular reproduction, new-growth, or regeneration), which manifests itself in three degrees (Fig. 95): (a) Destruction of the differentiated cells plus a hypertrophy of the regenerative cells; (b) hyperplasia of the regenerative cells, with or without their differentiation into specific cells, and (c) hyperplasia of the regenerative cells plus migration from normal anatomic environment, with or without partial differentiation.[2]

These being the biologic reactions of all living cells, it becomes essential to determine just what cells exist in the organ under consideration.

The prostatic gland (Fig. 96) as an organ of the genito-urinary system consists of the following tissues: (1) Glandular tissue, (2) fibrous connective tissue, (3) muscular tissue. To these may be added the tissues comprising the following sub-organs, which are a part of the gland: (1) Arteries and veins which are composed of endothelial, muscular, and connective tissues; (2) lymphatics, which consist of endothelial tissue and possibly a layer of slightly modified connective tissue of the stroma, and (3) nerves which consist of nerve-filaments and fibrous connective tissue. There are at least four other types of cells which may be found in the gland under normal conditions. These are leukocytes, lymphocytes, eosinophils, and mast cells. Whether or not these are always indicative of a pathologic process is still a disputed point.

The cells comprising the component tissues of the organ under discussion may be spoken of in their relation to the biologic reactions in the following terms:

Primary	adeno- fibro- myo-	Cytolysis.
	endothelio-	Atrophy.
Secondary	lympho- leuko-	
	eosino-	Hypertrophy.
Tertiary	neuro- angio-	Neoplasia.

This terminology possesses biologic, histologic, and clinical significance, although it does not represent a terminology which can be utilized as such for clinical diagnostic purposes.

The prostatic gland does not differ from other organs, such as the breast, in which organ it has been distinctly shown that detailed patho-

logic terminology, when utilized for clinical diagnosis, produced an extreme grade of terminologic inefficiency.[2]

It has been shown in the case of the breast that there must exist one terminology for the clinician and one for the pathologist, although these two must be parts of a comprehensive and logical conception of pathologic conditions. At present pathologic terminology is in the same stage of evolution which chemical terminology was in when Lavoisier was forced to invent a new terminology to express his own observations, which formed the basis of modern chemistry.

In regard to the prostatic gland, the structural arrangement of the
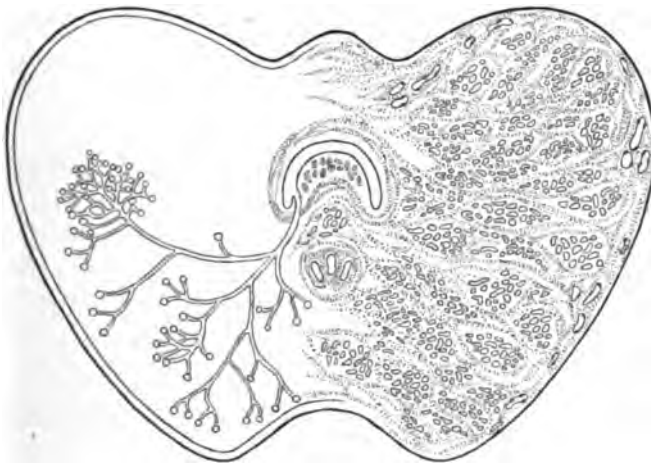
Fig. 97.—Diagrammatic mechanical distribution of the glandular units and their ducts.

tissues (Figs. 97 and 98), plus the general biologic reactions of cells, determines the descriptive terminology for the clinician and pathologist.

Without entering into a detailed anatomic description of the gland, it may be stated that the tissue which gives specificity to the organ is a direct outgrowth of the epithelium of the fetal urethra; it has become modified, however, in form and function during this evolution. The cells are arranged around spaces and form alveoli which empty their products of secretion into ducts which become assembled into larger ducts, which eventually discharge their contents in the folds of the urethra lying on each side of the colliculus seminalis. During the evolution of this peculiar structural adaptation many (10–40) such ducts have been formed, each of which is the unit outlet of a system of ducts and alveoli. Each system, therefore, forms an independent part

of the organ structurally, mechanically, physiologically, and patho-
logically. It is this structural and mechanical fact, with the biologic
reactions of the cells comprising the systems, which gives the irregular
shape to the various abnormal prostates which are found. Whether or
not the antagonistic agents arrive through the urethra, the circulatory
system, the lymphatics, or by direct contact with neighboring pathologic
organs, does not alter this fact.

PRIMARY CYTOPLASIA

A ---------Textocytes
  ---------Textoblasts

SECONDARY CYTOPLASIA

B ---------Textoblasts

TERTIARY CYTOPLASIA

C ---------Textoblasts
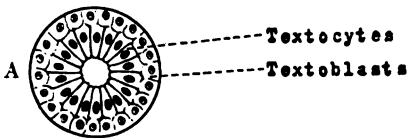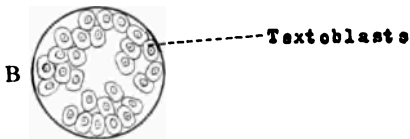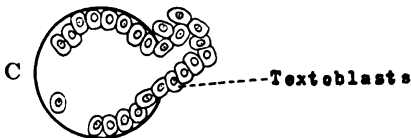
Fig. 98.—The three reactions to destruction of
textocytes in the mammary acinus. A, Primary
adenocytoplasia. B, Secondary adenocytoplasia.
C, Tertiary adenocytoplasia.

The specific glandular tissue
is supported by connective tissue
and is aided in its function by the
presence of smooth muscle, the
two latter tissues and those of the
blood-vessels and nerves also re-
acting according to biologic laws
to antagonistic agents.

In all reactions time plays an
important rôle, and in so doing
may alter the resultant pictures
of the tissues and consequently
the whole organ. Any one of the
fundamental reactions may occur
suddenly or gradually in so far as
time is concerned, and hence have
arisen the clinical terms "acute"
and "chronic."

The fact that one or more of
the structural groups of the gland
may be involved gives rise to con-
ditions which may be circum-
scribed or diffuse. As a result of
the fact that nature reacts to grad-
ual destruction by building up dense, protective connective-tissue barriers,
it is found that one or more structural groups may be surrounded by a
denser fibrous tissue or capsule which differentiates grossly parts of the
gland. This has given rise to the conception of tumors in the gland. They
are certainly tumors in the sense that they are enlargements, but their
presence is nevertheless due to one or more of the fundamental tissue
reactions, or to the mechanical principle of distention as a result of
obstruction to the normal outlets of fluid contents of spaces.

In view of these fundamentals, and the fact that cellular reactions

are usually microscopic reactions, especially in their incipiency, and the fact that clinical symptoms resulting from all forms of prostatitis are largely those arising from mechanical interference with the rest of the genito-urinary system, it becomes necessary to consider the fundamental reactions in their grosser aspect of gross effects which will be of service to those who deal with the organ from a macroscopic standpoint.

Aside from the conditions spoken of as "acute infections" the clinician and surgeon are interested in two conditions which they express under the terms of "hypertrophy" and "malignancy," both of which terms need some consideration from the standpoint of definition and description.

The term "hypertrophy," as used in conjunction with the terms adenomatous, myomatous, and fibromatous, describes an enlargement of the organ which is in reality a hyperplasia or neoplasia, and may be of epithelial, connective-tissue, or muscular origin. In fact, in such conditions there is an overgrowth of the regenerative cells of one or more of these tissues, plus a differentiation of the regenerative cells into either glandular tissue, connective tissue, or muscular tissue.

In the biologic terminology described in this paper "hypertrophy" is a secondary neoplasia or a neoplasia plus tissue differentiation, a condition which may occur in any or all of the structural groups of the organ. From a neoplastic standpoint the condition is clinically benign if differentiation is present. If there is an overgrowth of the regenerative cells without differentiation there is a question as to the benignancy or malignancy. If there is migration of the undifferentiated cells the condition is malignant. Such, from a clinical standpoint, may be grouped as follows:

Acute or Chronic	Circumscribed or Diffuse	Prostatic	adeno- fibro- myo- endothelio- neuro- angio-	Cytolysis. Atrophy. Hypertrophy. Neoplasia.

The only pathologic conditions expressed by these terms which are recognizable clinically are:

Acute or Chronic	Circumscribed or Diffuse	Prostatic		Cytolysis. Atrophy. Neoplasia.

Occasionally, the clinician may be able to recognize that a malignant neoplasia exists. The rest of the complete terminology can be filled out only by the pathologist.

It may seem strange that the writer has said nothing about carcinoma, adenoma, fibroma, lymphosarcoma, rhabdomyoma, spindle- and

small-cell sarcoma, malignant rhabdomyoma, adenosarcoma, angio-
sarcoma, myxosarcoma, and epithelioma, all of which terms and their
indicative conditions have been described in the literature. Briefly it
may be stated that these terms represent conditions described in the
new terminology. They are, to use the language of Pattison Muir
in describing alchemical terminology, "based on far-fetched fanciful
analogies"; in that language the word did not call forth any just and
clear idea—the idea did not depict any definite fact.

Perhaps it is too early to make a prophecy that such terms as sarcoma
and carcinoma will be relegated to that extinct group of medical terms
which embraces such words as emphyma, cancer vulgaris, scrophula
vulgaris, ulcer vitiosum, and marasmus atrophia.

A modern terminology must be consistent with and descriptive of
biologic, histologic, and clinical facts in order to be efficient in this day of
efficiency.

Any of the conditions of the prostatic tissues which have been here-
with described may be clinically malignant or benign, since both terms
are purely clinical and are not histologically descriptive. A benign
infectious or neoplastic condition today may be a malignant condition
later, without any living man being able to definitely and positively
state in advance that it will or will not be. It seems wise for the clinician
and the pathologist to adhere closely to that which they can see. If
this be done, no scientific clinician will attempt to utilize a detailed
descriptive pathologic terminology for things he cannot see.

REFERENCES

1. MacCarty, W. C.: The histogenesis of cancer of the breast and its clinical significance.
     Surg., Gynec. and Obst., 1913, xvi, 441–459.
     Histogenesis of carcinoma in ovarian simple cysts and cystadenoma. Collected
     Papers, Mayo Clinic, 1913, v, 380–390.
     Clinical suggestions based upon a study of primary, secondary (carcinoma?) and
     tertiary or migratory (carcinoma) epithelial hyperplasia of the breast. Surg.,
     Gynec. and Obst., 1914, xviii, 284–289.
     Precancerous conditions. Jour. Iowa State Med. Soc., 1914–15, iv, 1–11.
     Notes on the regularity and similarity of cancer cells. Collected Papers, Mayo
     Clinic, 1914, vi, 600–602.
     The histogenesis of cancer of the stomach. Am. Jour. Med. Sc., 1915, cxlix, 469–
     476.
     New facts about cancer and their clinical significance. Surg., Gynec. and Obst.,
     1915, xxi, 6–8.
     The biological position of the carcinoma cell. Pan-Am. Surg. and Med. Jour.,
     1915, xx.
     The evolution of cancer. Collected Papers, Mayo Clinic, 1915, vii, 903–917.
     MacCarty, W. C., and Mensing, E. H.: The relation between chronic mastitis and
     carcinoma of the breast. St. Paul Med. Jour., 1916, xviii, 164–167.
     A new classification of neoplasms and its clinical value. Am. Jour. Med. Sc., 1916,
     cli, 799–806.
2. MacCarty, W. C., and Broders, A. C.: Studies in clinicopathologic standardization and
     efficiency. Surg., Gynec. and Obst., 1917, xxiv.

ABSTRACTS OF STUDIES ON THE OVARY OF THE SPERMOPHILE (SPERMOPHILUS CITELLUS TRIDECEMLINEATUS), WITH SPECIAL REFERENCE TO THE CORPUS LUTEUM*

DELLA DRIPS

Up to 1906, practically all the literature on the corpus luteum had to do with the histologic origin and consequent structure at various succeeding periods in its life cycle. The writings of Sobotta and Cohn practically established the epithelial nature of the luteal cells and the glandular character of the structure as a whole. From 1906 to 1912 most of the papers written were reports of experimental studies undertaken to prove that the corpus luteum is the gland of internal secretion in the ovaries, and that, through this secretion, the luteal structure produces specific effects on other organs, particularly the uterus. In spite of the many criticisms directed against his work, Fraenkel still stands preëminent among the experimental workers who established beyond a doubt the foregoing hypothesis.

Since 1910 efforts have been put forth by investigators actually to demonstrate this secretion in the corpus luteum. Van der Stricht comes nearer the goal than any other. The greater part of recent literature, however, concerns the extract of the corpus luteum, its chemical constituency, its physiologic action, and its clinical value.

In the summer of 1914, while I was studying microscopic sections of the various tissues and organs of the spermophile, the relatively immense size of the ovaries, compared with those observed the previous spring, strikingly presented itself. On further comparison it was very evident that this great increase in size had been brought about by a

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In its original form the thesis consists of four divisions: I. Literature; II. The ovarian cycle; III. Experimental studies, and IV. Summary and conclusions. In abstracting, the first division was practically omitted, the second division greatly contracted, the third division completely omitted, and the fourth division fully given. The entire article will appear in The American Journal of Anatomy.

growth in the corpora lutea only. One ovary contained 11 of these bodies; there remained only a framework of ovarian stroma, with a few atretic follicles.

From observations that had been going on it was known that these spermophiles had given birth to young about a month before. According to most writers, degeneration of the luteal cells begins not later than birth. Here were what looked like actively secreting cells a month after birth. Thereupon it was decided to try out some differential stains on these luteal cells at every stage in their life history, and to study the complete ovarian cycle in the spermophile with a view to gaining some accurate information of the origin, development, life history, and function of the corpora lutea of the ovary.

In the spring of 1915 numbers of spermophiles were captured. But not having realized how very soon the animals become impregnated after coming out of hibernation, no strenuous efforts were made to obtain them until they were quite numerous in the fields, and consequently they were found to be either in advanced stages of pregnancy or lactating. However, all the animals that could be obtained were used for a study of the ovarian cycle through the summer and fall, until hibernation began.

Several animals were sacrificed each week. They were killed quickly with ether and bleeding. The ovaries were immediately placed in one of several fixatives—10 per cent formalin, Zenker's fluid with acetic acid, Bensley's formalin-Zenker, and Bensley's acetic acid bichromate. Many stains were experimented with. After considerable study of the fixed and stained sections, it was decided that for the problem in hand two fixatives seemed best, Bensley's formalin-Zenker and Bensley's acetic osmic bichromate—the former particularly for the nuclear structures and the latter for the elements in the protoplasm. In all the work of the past spring (1916) one ovary of each animal sacrificed was routinely placed in formalin-Zenker and the other in acetic osmic bichromate.

Of the sections fixed in Zenker, the best results were obtained with a modified Weigert stain (copper-chrome-hematoxylin), Ehrlich's hematoxylin and eosin, Mallory's connective-tissue stain, and Bensley's acid fuchsin and methyl-green. A few sections of each series were prepared with these stains.

Of the sections fixed in acetic osmic bichromate, one of each series was stained with the Weigert stain, and several with the acid fuchsin

and methyl green of Bensley. Complete paraffin serial sections were made of all the ovaries studied.

The spermophiles went into hibernation about the middle of October, although many of them became partially torpid earlier than this. The next spring it was determined to get them early enough. The frost was not out of the ground until about April 15. With a great deal of difficulty the females were obtained while in rut, and every day through the period of pregnancy, which was found to be about twenty-eight days. Two or more were sacrificed each day.

The ovarian cycle was now completed. Ovaries were at hand for every week of the year except during the hibernation period, when only a sufficient number of animals was sacrificed to make sure there were no changes taking place in these organs. For the period of pregnancy, a time which is especially related to ovarian activity, there were ovaries for even fractions of a day.

The period of rut evidently follows immediately on the awakening of the spermophiles in the spring. Ovulation follows on coitus. Most of the females are impregnated in a very short time. The period of pregnancy follows. From the time of ovulation until about September 1 the ovaries contain corpora lutea. These approach their greatest size about July 1. By September 15 the large corpora lutea have disappeared. With the disappearance of the corpora lutea there is a very noticeable rapid growth of the follicles, together with a noticeable decrease in the size of the whole ovary. The ovaries, which in July consisted almost entirely of large corpora lutea with a small amount of ovarian stroma containing a few atretic follicles, by September 15 contained no corpora lutea, but instead many medium and good-sized growing follicles containing very little liquor folliculi, but filled with mitotic figures.

The ovaries of the fall, winter, and spring, then, contain no corpora lutea. Occasionally some remains of these bodies of the previous year may be found, but this is very unusual. So when coitus takes place during rut and the follicles burst and become transformed into corpora lutea, these new bodies are the only corpora lutea in the ovary. They are all produced simultaneously, and they also develop simultaneously if they are not abnormal in some way.

The picture of the ovary changes when fertilization brings on pregnancy. From this time on until the period of the growing follicles is reached in the late summer the ovaries contain corpora lutea. These

are the predominating structures in the ovaries of the spring and summer. The changes which take place in these organs during this period have to do with the corpora lutea principally. The following descriptions of ovaries will be attempts at picturing them with corpora lutea of various ages. As this study is very largely concerned with these luteal structures, they will be described in considerable detail.

EXPERIMENT 268–16 (SPERMOPHILE 303).—Captured May 3, 1916. Sacrificed the same day. Weight, 112 gm.

Gross observations.—There are no visible signs of pregnancy in the uterus except congestion. The ovaries contain several slightly raised, small spherical bodies, which resemble mature follicles except that they are red or pink instead of colorless.

Microscopic observations of the left ovary.—Fixative, acetic osmic bichromate. Stain, acid fuchsin and methyl-green. This ovary contains five luteal bodies, three of which are normal and two of which are not. Besides these, there are several growing, medium-sized follicles, no large ones, quite a number of small atretic follicles, and a few primordial ova. The interstitial cells are not as conspicuous in this ovary as they were in some of the ovaries of early pregnancy. All the blood-vessels and sinuses in the medullary portion of the ovary are very much dilated. Most of the ovary is made up of the five corpora lutea. Serial sections of the three normal ones show them to be of different sizes—from 0.7 mm. by 0.8 mm. in diameter to 1.3 mm. by 0.1 mm., depending on the amount of blood which they contain, for practically all the young corpora lutea contain blood in their centers (Fig. 99). A hemorrhage from a blood-vessel in the wall of the follicle must occur as the follicle bursts. The exact point of this bursting cannot be determined in any of these structures. Each luteal body is surrounded by a very thin connective-tissue capsule—no doubt the same *theca externa* which surrounded the follicle. From this thin capsule to the central core of blood are massed the luteal cells. They seem to have no definite arrangement. Among them may be seen numerous fibroblasts and endothelial cells. These are most numerous about the periphery of the

Fig. 99.—(Experiment 268–16.) Fixative, acetic osmic bichromate; stain, acid fuchsin and methyl-green. Cross-section of a very early corpus luteum (× 80).

central mass of blood. Some are already making their way into it.
The cells all seem to have their axes directed radially, as if they were approaching the central mass of blood from the periphery of the luteal body. The luteal cells are of various sizes and shapes. Some are spindle-form and some polygonal, but the majority are spherical or oval. There is one specific characteristic of all young luteal cells, and that is the existence of spherical granules in their protoplasm. In the sections fixed in Bensley's acetic osmic bichromate, and stained with acid fuchsin and methyl-green, these granules are strikingly brought out (Figs. 100 and 101). They are colored a brilliant red. Their sizes vary somewhat, but they are all spherical. The protoplasm of some cells is so full of these granules that it resembles a homogeneous red secretion, but
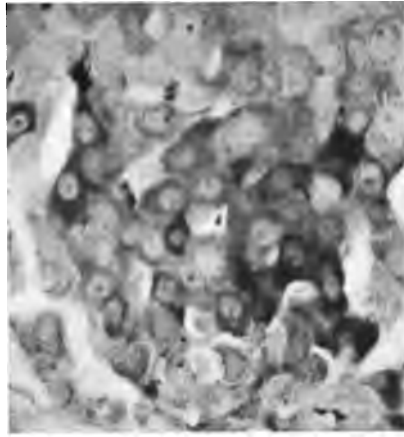
Fig. 100.—(Experiment 268–16.) Fixative, acetic osmic bichromate; stain, acid fuchsin and methyl-green. Portion of a very early corpus luteum. Note the luteal cells filled with so many granules that their protoplasm appears a homogeneous red.

on examination with very high power the separate granules may be seen. In many cells where the granules do not fill the protoplasm they are grouped about the nucleus, leaving a narrow, clear zone about the periphery of the cell. The nuclei take the green stain and are strikingly brought out against the red granules. Each nucleus contains one or two good-sized, bright, red-staining nucleoli. The chromatin threads stain green and do not show very well with this stain.

Fig. 101.—(Experiment 366–16.) Fixative, acetic osmic bichromate; stain, acid fuchsin and methyl-green. Portion of a corpus luteum of the red granule stage. Compare the size of the cells with those of Fig. 100.

EXPERIMENT 293–16 (SPERMO-PHILE 328).—Captured May 4, 1916. Both ovaries were removed May 6, 1916. Weight, 119 gm.

Gross observations.—The fetuses in the uterus measure about 2 mm.
in length, which makes the luteal bodies in the ovaries older than those previously described.

Microscopic observations of the right ovary.—Fixative, formalin-Zenker. Stain, acid fuchsin and methyl-green. This ovary contains six corpora lutea. These luteal bodies appear differently, due principally to the rapid growth which has been going on among the fibroblasts and endothelial cells. The ovaries suffered some congestion through the manipulation of removal, and this helps to show the great numbers of capillaries and blood-vessels that have been formed in a short time. The central mass of blood is undergoing rapid organization. No doubt the presence of this blood with its serum and fibrin is the great attractive force which aids in the complete formation of the luteal body. Fibroblasts and endothelial cells are always attracted by serum and fibrin. As soon as the hemorrhage occurs in the follicle, they start in to organize it. This is evident from the radial direction which the axes of the fibroblasts all take very early. As they go into the center the transformed epithelial cells of the follicle are carried in by them. Endothelial cells grow in, and thus very early there is formed in the corpus luteum a complex system of blood-vessels and capillaries, as is seen in sections of this ovary.

EXPERIMENT 296–16 (SPERMOPHILE 331).—Captured and sacrificed May 6, 1916. Weight, 146 gm.

Gross observations.—The fetuses in the uterus are 1 cm. in length, which lead us to expect to find changes in the corpora lutea of the ovaries.

Microscopic observations of the left ovary.—Fixative, acetic osmic bichromate. Stain, acid fuchsin and methyl-green. The size of the luteal structures has increased. There are two in this ovary, one measuring 0.9 mm. by 0.9 mm., and the other, 1 cm. by 0.8 mm. The most noticeable feature of this later luteal body is the absence of any blood in the center. Instead, there is a core of connective tissue. The size of this connective-tissue core depends evidently on the amount of hemorrhagic material there is to organize. In some bodies the core is much larger than in others. Very perceptible strands of connective tissue run from this central mass to the capsule, inclosing columns of luteal cells. Cross strands have developed also, so that connective-tissue strands seem to be enveloping each cell. There is a complete capillary network following the arrangement of the strands of connective tissue. Good-sized blood-vessels are located about the periphery of the structure. Several smaller ones are present in the central connective-tissue core. There are several sinuses about the periphery lined with endothelium which appear to contain lymph. The luteal cells themselves have increased in size. Many more have taken on an oval shape and are lying with their long axes perpendicular to the capsule. The same red granules are still present in the protoplasm. These do not seem to be quite as numerous in the cells, which fact is in part due, no doubt, to the increased size of the latter. The granules are now found scattered throughout the protoplasm, the clear zone about the periphery

of the cell having disappeared. The granules show more difference in size than formerly, but they are still all spherical. The nuclei have not changed. In a few cells there is a clear space in the protoplasm on one side of the nucleus.

EXPERIMENT 355–16 (SPERMOPHILE 375).—Captured May 20, 1916. Both ovaries were removed May 22, 1916. Weight, 126 gm.

Gross observations.—The fetuses in the uterus are 1.5 cm. in length.

Microscopic observations of the right ovary.—Fixative, acetic osmic bichromate. Stain, acid fuchsin and methyl-green. There are six corpora lutea in the right ovary, measuring about 0.8 mm. by 0.9 mm. in diameter. Something is noted in the luteal structures in this ovary which has not been seen before, namely, that there are present in the cells close to the periphery some osmic-stained droplets. The size of the corpus luteum and the size of the individual cells is about the same as that of Spermophile 331. There is a slight increase in the number of red granules in the cells. The clear space next to the nucleus is present in many more cells. The osmic-stained droplets are located at the periphery of the cell. They are very large compared with the red granules. They vary somewhat in size, but not in shape; all are spherical. Of course, in sections fixed with formalin-Zenker and stained with the various stains which were used, these lipoid droplets appeared as vacuoles. But they could be easily recognized by their corresponding size and location in the cells. For convenience, these droplets will be called lipoid droplets, because they certainly are a lipoid product. They do not appear in the luteal cells before the fetus is about 1.5 cm. in length, or about fourteen days old, that is, until the period of pregnancy is half over. These droplets make up the "lutein" of the corpus luteum which has been described for many years and which has given the corpus luteum its name.

When the lipoid droplets appear in the cells, the period of the red granules is waning. The latter seem to reach their crisis of abundance when the fetus measures about 8 mm. in length. But the granules are still very abundant in the cells until the lipoid droplets begin to appear. From this time on the former grow fewer and the latter increase in number, as will be shown, until they too reach a crisis of abundance and then decline.

EXPERIMENT 363–16 (SPERMOPHILE 383).—Captured and sacrificed May 24, 1916. Weight, 140 gm.

Gross observations.—The animal was in labor when killed. The uterus still contains two live fetuses, four having already been born. The crown rump measurement of a fetus is 4–5 cm.

Microscopic observations of the left ovary.—Fixative, acetic osmic bichromate. Stain, acid fuchsin and methyl-green. The luteal structures in the ovaries of this animal show some changes over those previously described (Fig. 102). There are four of them. They have

increased slightly in size, measuring 0.9 mm. by 0.9 mm. and the indi-
vidual cells have increased correspondingly.   Still more noticeable than
their increase in size is the regularity of their oval form and the uni-
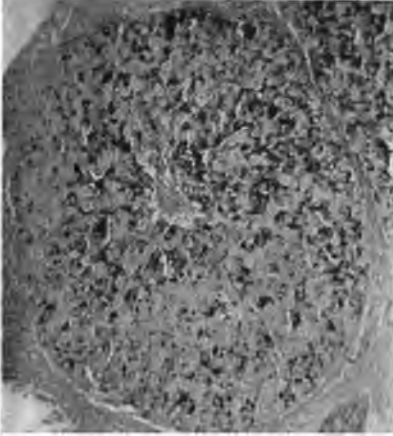
Fig. 102.—(Experiment 363–16.) Fixative, acetic osmic bichromate; stain, acid fuchsin and methyl-green.   Cross-section of a corpus luteum at parturition (× 80).
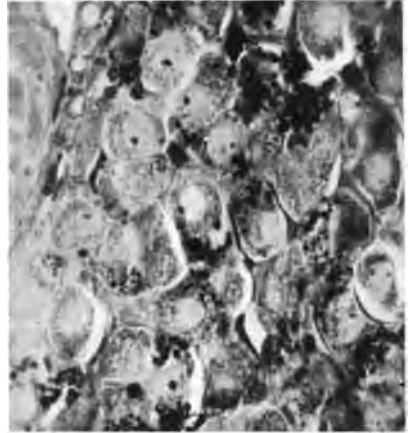
Fig. 103.—(Experiment 363–16.) Fixative, acetic osmic bichromate; stain, acid fuchsin and methyl-green.   Portion of a corpus luteum at parturition. Note the black lipoid droplets at the periphery of the luteal cells.   Compare their size with that of the red granules.   There is a well-formed connective-tissue framework (× 650).

Fig. 104.—(Experiment 444–16.)   Fixative acetic osmic bichromate; stain, acid fuchsin and methyl-green.   Cross-section of an ovary about eight weeks after parturition (× 20).
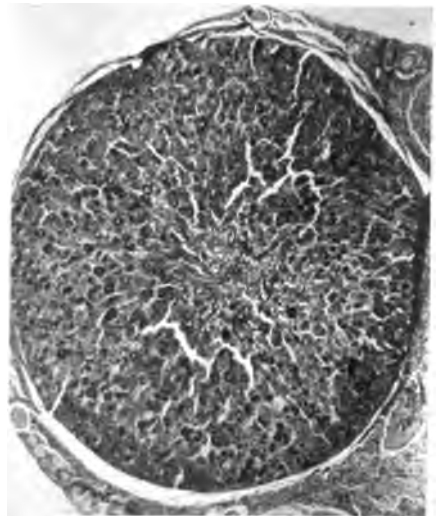
Fig. 105.—(Experiment 413–16.) Fixative, acetic osmic bichromate; stain, acid fuchsin and methyl-green. Cross-section of a corpus luteum six weeks after parturition (× 80).

formity with which all their axes point in a radial direction.   This seems
to be due to an increased amount of connective-tissue framework, which,
from the first, has seemed to govern the position and shape of the cells.
The increase of connective-tissue framework has been accompanied by
an increase in the size of the blood-vessels and capillaries.   In the luteal
cells (Fig. 103) the red granules have decreased still more than in the
cells last described, and this is very general throughout the structure.
The lipoid droplets are much more numerous in all the cells. In fact, it
seems hard to tell which is the predominant product of the cells, the red
granules or the black droplets.   The nuclei of these cells are slightly

Fig. 106.—(Experiment 439–16.) Fixative, acetic
osmic bichromate; stain, acid fuchsin and methyl-
green.   Cross-section of a corpus luteum about eight
weeks after parturition (× 80).
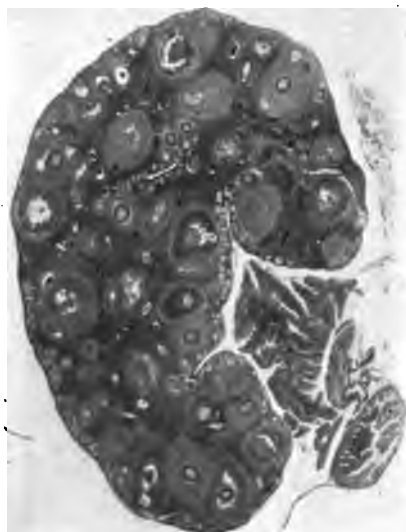
Fig. 107.—(Experiment 346–15.)   Fixative, forma-
lin Zenker; stain, brasilin, and wasserblau.   Cross-
section of an ovary of the late summer (× 30).

larger than the ones of the preceding description.   Otherwise, they are
the same.   Most writers have agreed that degeneration of the corpus
luteum begins about the time of birth.   None is in evidence here.
Several writers have stated that the principal reason for their belief was
the entrance into the cells of osmic-staining droplets which they con-
sidered to be evidences of fatty degeneration in the cells.   It would not
seem, from the nuclear characteristics of the cell nor from the color,
shape, and the regular size of the droplets, that they could be fatty
degeneration products, especially when compared with the true fatty
degeneration which occurs much later in the life history of the corpus
luteum and which will be described accordingly.

EXPERIMENT 412–16 (SPERMOPHILE 415).—Captured and sacrificed July 1, 1916. Weight, 125 gm.

Gross observations.—The ovaries are the largest yet seen, owing to the comparatively immense size of the corpora lutea. These are now of a yellowish-cream color, and stand out prominently so that the ovary looks as if it were made up of several spherical bodies, 1.5 mm. in diameter. Any other ovarian tissue except that holding the spherical bodies together can scarcely be distinguished. There are three corpora lutea in the right ovary and four in the left, which numbers correspond to the tiny white spots marking the former placental sites in the uterus.
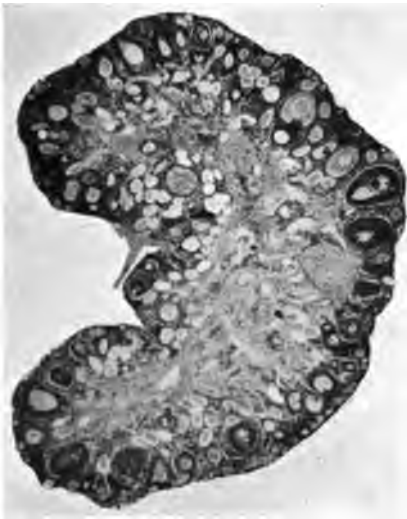
Fig. 108.—(Experiment 219–16.) Fixative, formalin Zenker; stain, hematoxylin and eosin. Cross-section of a normal ovary of early spring (× 25).

Fig. 109.—(Experiment 246–16.) Fixative, formalin Zenker; stain, acid fuchsin and methyl-geren. Cross-section of an ovary of rut (× 25).

EXPERIMENT 413–16 (SPERMOPHILE 416).—Captured and sacrificed July 3, 1916. Weight, 157.3 gm.

Gross observations.—The right ovary appeared grossly just like that of Spermophile 415.

Microscopic observations of the left ovary.—Fixative, acetic osmic bichromate. Stain, acid fuchsin and methyl-green. The corpora lutea are much larger than those previously described (Figs. 104 and 105). They measure 1.1 mm. by 1.5 mm. in diameter (1.7 mm. by 1.3 mm., grossly, some shrinkage). The luteal cells are correspondingly larger, and their protoplasm is absolutely full of a mass of lipoid droplets. This is seen to advantage in the unstained sections. In the stained sections the cells appear more or less honeycombed, according to the amount of lipoid which has been dissolved out. These lipoid droplets are very

uniform in size and are dark brown, quite a different color from the black fat droplets of fatty degeneration. The red granules are gone. Where there is any protoplasm visible, it appears granular and pinkish-gray in color. The nuclei of the cells appear slightly smaller than formerly, but this apparent decrease in size is evidently due to the increase in the size of the cells, for the nuclei are no smaller by measurement. The location of the nucleus in the cell is either in the center or to one side of the center. The nucleolus stands out large and bright and the chromatin strands appear as they did. There are no apparent degenerative changes. Beside the three corpora lutea in this ovary, there are six or seven medium-sized normal growing and three atretic

Fig. 110.—(Experiment 275–16.) Fixative, formalin-Zenker; stain, hematoxylin and eosin. Cross-section of an ovary very early in pregnancy (× 25).

Fig. 111.—(Experiment 277–16.) Fixative, formalin-Zenker; stain, hematoxylin and eosin. Cross-section of an ovary early in pregnancy after the corpora lutea have become partially organized (× 25).

follicles. There are no large follicles or even any of good size. A few primordial ova are present, fewer than in any of the ovaries described thus far, and no interstitial cells can be distinguished as such (Fig. 104).

EXPERIMENT 439–16 (SPERMOPHILE 436).—Captured June 23, 1916. Sacrificed July 15, 1916. Weight, 194.2 gm.

Gross observations.—The uterus still shows several tiny white spots marking the placental sites. It is otherwise normal. The ovaries appear to contain corpora lutea, but these latter are certainly much reduced in size over those of Spermophile 416. They appear congested or of a reddish-yellow color.

Microscopic observations of the left ovary.—Fixative, acetic osmic bichromate. Stain, acid fuchsin and methyl-green. The corpora lutea

are much smaller (Fig. 106).   They measure 0.7 mm. by 0.8 mm. and
0.9 mm. by 0.9 mm.   The cells are smaller.   The protoplasm of the
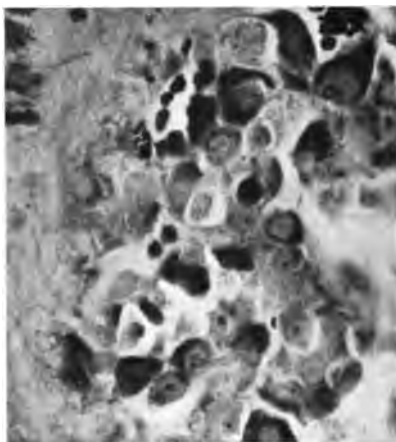
Fig. 112.—(Experiment 268–16.) Fixative, acetic
osmic bichromate; stain, acid fuchsin and methyl-
green.   Section through the wall of corpus luteum
showing untransformed cells of the stratum granulo-
sum of the follicle persisting among the early luteal
cells (× 600).

Fig. 113.—(Experiment 268–16.) Fixative, acetic
osmic bichromate; stain, acid fuchsin and methyl-
green.   Cross-section of a corpus luteum cyst (×80).

Fig. 114.—(Experiment 275–16.) Fixative, forma-
lin-Zenker; stain, hematoxylin and eosin. Cross-section
of a corpus luteum with a retained ovum (× 80).

Fig. 115.—(Experiment 293–16.) Fixative, forma-
lin-Zenker; stain, hematoxylin and eosin. Cross-section
of a corpus luteum hemorrhagic cyst (× 80).

cells contains no red granules and very few lipoid droplets or any honey-
combing suggestive of these.   It has a grayish, granular appearance.
Something is present, however, which has not been seen before, and that

is fat. Scattered here and there throughout the luteal structure, fat globules, characteristic of fatty degeneration, are present in the protoplasm of the cells. They are of various sizes and take on a characteristic black color with the osmic acid in the acetic osmic bichromate fixative. The nuclei of the cells show degeneration changes. The nucleolus has disappeared in some cells and in others appears pale and fringed. The chromatin strands are fewer and appear clumped in some cells. One striking new feature in the luteal structure is the great increase in the size of the blood-vessels and capillaries. The congestion of blood is not common to the whole ovary, but is only in the corpus luteum. The vascular change is apparently one factor in the disappearance of the luteal body.

EXPERIMENT 515–16 (SPERMOPHILE 458).—Captured August 18, 1916. Sacrificed August 21, 1916. Weight, 190 gm.

Gross observations.—There are no evidences of placental sites in the uterus. There are no signs of corpora lutea in the ovaries.

Microscopic observations of the left ovary.—Fixative, acetic osmic bichromate. Stain, acid fuchsin and methyl-green. The left ovary shows three luteal structures. The largest measures 0.8 mm. by 0.8 mm. No red granules or lipoid droplets are discernible. The greenish-gray granular protoplasm is everywhere filled with various-sized fat droplets. In some cells these fat droplets are so large that they occupy nearly the whole cell, squeezing the degenerated nucleus out to one side of the cell. The nuclei are so degenerated that no chromatic strands or nucleolus are recognizable as such. What is left of the nucleus takes the acid fuchsin rather than the methyl-green stain. All the blood-vessels and capillaries are markedly dilated. There is a marked increase of connective tissue throughout the body. The thin capsule of connective tissue which before surrounded the luteal structure seems to have disappeared in places, making it appear as if the connective tissue of the body were continuous with that of the ovary around it. This connective-tissue invasion is evidently another factor in the disappearance of the corpus luteum. Three factors, then, are associated with the disappearance of the corpora lutea in the ovaries—cellular degeneration, vascular dilatation, and connective-tissue invasion.

SUMMARY AND CONCLUSIONS

The results obtained from the histologic and experimental investigations carried on may be summarized as follows:

1. In the spermophiles, ovulation occurs only once a year—during the rutting season in the early spring. Ovulation is dependent on the stimulus of coitus, for no corpora lutea were found in the ovaries of animals which were kept from the males.

2. The corpora lutea cannot be responsible for the phenomena of rut, for they are not present in the ovaries at this time.

3. The corpora lutea develop and pass through their normal cycle after ovulation, whether fertilization follows or not.

4. While the corpora lutea are present in the ovaries, especially during the two months following parturition, the process of developing and ripening the follicles is at a standstill.

5. If the uterus is removed after conception, the corpora lutea do not begin to degenerate, but pass through their normal cycle. No effects were noted in the ovaries.

6. Removal of the uterus at any time does not produce noticeable effects on the ovaries even after a year's time.

7. Double ovariectomy performed at any time during the period of pregnancy interrupts gestation. If the operation is performed after a little more than the first half of pregnancy, the placentas with the fetuses simply degenerate. The involution of the uterus in these cases is very abnormal. If both ovaries are removed late in pregnancy, the animal aborts and the uterus undergoes a much more normal involution. The removal of only one ovary does not interrupt the pregnancy.

8. Double ovariectomy at any time prevents the recurrence of the cyclic changes in the uterus and produces an atrophy of the organ scarcely noticeable within a year.

9. The corpora lutea apparently do not influence the development of the mammary gland. When the uterus was removed very soon after conception, before any signs of pregnancy could be noted grossly in the uterus, and before any development of the mammary glands could be noted grossly, the developing corpora lutea in the ovaries produced no development in the mammary glands. This would seem to substantiate the work of Lane-Claypon and Starling, who attribute to the fertilized egg the stimulus for the development of the mammary glands.

10. The corpus luteum of the spermophiles derives its elements from the follicle just as Sobotta states occurs in the mouse. The luteal cells are the transformed granulosa cells of the follicle. The connective-tissue and vascular network are derived from the cells of the internal theca, which spends itself entirely in their formation. The capsule of connective tissue surrounding the luteal structure is the same external theca which surrounds the follicle. The microscopic pictures of the corpora lutea in the succeeding stages of their development correspond also to Sobotta's descriptions. It may be well to emphasize the com-

plexity of the vascular network throughout the luteal structure which, when it is completed, brings every luteal cell in intimate contact with the blood-stream.

11. The life cycle of the corpus luteum is made up of three distinct phases. First, the phase characterized by the presence of great numbers of red granules in the protoplasm of the luteal cells. This phase embraces a period dating from the bursting of the follicle and covering the entire period of pregnancy. From a point of time very shortly after the bursting, the protoplasm of the luteal cells shows these red granules, which become more and more abundant until they seem to reach a crisis of abundance when the organization of the luteal structure is about perfected, which is not until the placental swellings have reached a length of about 8.5 cm. From this time on the granules seem very gradually to decrease in number in the cells until parturition, when there is a sudden considerable reduction in their number. Some are found in the cells, however, even as late as the fourth week after parturition. Second, the phase characterized by the presence of many lipoid droplets in the protoplasm of the luteal cells. This phase begins some time before parturition and lasts for about six weeks afterward. About the fourteenth day of pregnancy, when the placental swellings in the uterus measure 1.5 cm. to 2 cm. in length, the lipoid droplets usually begin to make their appearance at the periphery of the luteal cells, next to the capsule of the corpus luteum. They increase in number until, at the time of parturition, they are quite noticeable in the cells, being found scattered all through the protoplasm among the red granules. After parturition there seems to be a more rapid increase in the number of lipoid droplets, which coincides with the sudden decrease in the number of red granules previously noted. With this increase in lipoid content the cells, which, from the beginning, have been growing constantly larger, seem to begin to hypertrophy more rapidly. The luteal cells are largest and contain the greatest amount of lipoid about six weeks after parturition. In two more weeks practically all the lipoid has disappeared from the cells and they are beginning to show evidences of degeneration. Third, the phase of regression. This period begins about eight weeks after parturition and lasts for four weeks. By the last of August the corpora lutea have disappeared from the ovaries. This phase is characterized by a fatty degeneration of the luteal cells by an increased vascularization and a connective-tissue invasion. From these results

the following conclusions were drawn as to the functions of the corpora lutea in the ovaries of spermophiles:

The corpora lutea fix the periods of estrous by preventing the development and the ripening of the follicles until the time for the next rutting season is at hand.

The corpus luteum is a gland with two internal secretions, both of which have specific effects on the uterus, one bringing about the changes incident to pregnancy and the other effecting the normal involution of the organ. The first internal secretion is represented in the luteal cells during the period of pregnancy by granules which are very similar in their location and staining reactions to the granules in the A cells of the islands of Langerhans, the glands of internal secretion of the pancreas, described by Bensley. The granules of the luteal cells, however, are much larger than those of the A cells, being very easily seen with high powers of the microscope. No mitachondrial granules or filaments could be observed, perhaps because of the abundance of the granulations in the protoplasm. These luteal cell granules are very much like other secretion granules described by various writers as occurring in the secreting serous cells of several glands of the body.

The majority of writers have agreed that there is no fatty product demonstrable in the corpus luteum of several species of animals and man in the very early stages.· They all seem to have been of the same opinion that the activity of the ovarian gland of internal secretion begins with the appearance of the lipoid droplets in the cells. These lipoid droplets were considered by them to be the evidence of the secretory activity of the corpus luteum. Its period of activity would then begin when the droplets begin to appear in the cells, which time varies with different species, but in all seems to be about the time of the fixation of the blastocyte. This activity lasts, they consider, for varying periods in different species. In the rabbit, Cohn, Fraenkel, and Niskoubina consider that it lasts for nine or ten days; regression sets in about the fifteenth day. Van der Stricht says that in the bat the lipoid droplets are in much greater abundance during the second half of the period of pregnancy and that regressive changes do not begin until the period of pregnancy is over. Miller says there is no neutral fat in the human corpus luteum until regression sets in at birth. Because the first-mentioned group of men found that double ovariectomy did not cause abortion in rabbits after the fifteenth day, and did so earlier than this, they considered this lipoid secretion related to changes in the uterus

occurring between the fourth and fifteenth days after coitus, or between the time of the fixation of the blastocyte and the middle of the period of pregnancy.

Van der Stricht seems to have been the first to conceive of the presence of a secretion in the luteal cells prior to the appearance of the lipoid droplets which coexists with them for some time after their appearance. He judges of the presence of this secretion in the cells from its presence in the near-by intercellular spaces and lymphatics. The latter, according to van der Stricht, are the avenues of excretion of both the serous and the lipoid secretions.

In spermophiles, the lipoid product does not begin to appear in the luteal cells until the period of pregnancy is half over and is not very abundant until after birth. As far as these animals are concerned, then, the lipoid product is not the active substance of the corpus luteum, which has specific effects on the uterus during pregnancy. This active substance is rather a secretion represented in the cells by the secretory granules previously noted, which are of a very different nature from the lipoid droplets.

The second internal secretion which is represented in the luteal cells by lipoid droplets and which formerly has been considered the secretion which is responsible for the changes occurring in the uterus incident to pregnancy, must be considered, as far as the spermophiles are concerned, at least, as having another function. There seems to be some relationship in these animals between the period of greatest abundance of the lipoid product in the cells and the period of regression and atrophy in the uterus. The uterus of the spermophile atrophies very slowly—much more so than in animals that bear several litters of young every year. The atrophy is not completed until six or seven weeks after parturition, about the time when the lipoid product reaches its crisis of abundance in the cells and begins to disappear. Another result which substantiates the theory that the lipoid secretion brings about the normal involution of the uterus is the very abnormal, even pathologic, process which goes on in the uterus following the removal of both ovaries during all but the more advanced stages of pregnancy. During the first half of the period of pregnancy there is no lipoid in the corpora lutea, which, according to this theory, would account for the pathology in the uterus following double ovariectomy. If the ovariectomy is performed late in pregnancy, after the lipoid droplets have become quite abundant in the luteal cells, the animal aborts and the uterus undergoes an involution

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more nearly like the normal, due to the specific effect of the lipoid secretion which is already present in the circulation. Mulon thought the lipoid of the corpus luteum had an antitoxic action toward the poisons elaborated in the development of the fetuses. It would seem more reasonable to suppose that it neutralizes the toxic products produced in normal involution, which would be only a part of its function as a specific agent in effecting this normal involution of the uterus.

It may be added, in closing, that the two luteal secretions are undoubtedly emptied into the blood-stream in these animals. An observation of the elaborate capillary network of these structures could lead to no other conclusion. Lymphatic sinuses are demonstrable in the corpora lutea, but they are found only near the capsule in the proximity of the larger blood-vessels. There is no anatomic evidence for concluding that the secretions are carried away by the lymphatics.

REFERENCES

1. Alquier, L., and Theuveny, L.: État de l'evaire de chiennes ayant subi l'extirpation partielle ou totale de l'appareil thyro-parathyroidien. Compt. rend. Soc. de biol., 1909, lxvi, 217–219.
2. Ancel, P., and Bouin, P.: Sur la fonction du corps jaune; action du corps jaune vrai sur l'uterus. Compt. rend. Soc. de biol., 1909, lxvi, 505–507.
3. Ancel, P., and Bouin, P.: Sur le follicule de De Graaf mur et la formation du corps jaune chez la chienne. Compt. rend. Soc. de biol., 1908, lxv, 314–316.
4. Ancel, P., and Bouin, P.: Sur les homologies et la signification des glandes a sécrétion interne de l'ovaire. Compt. rend. Soc. de biol., 1909, lxvii, 497, 464–466.
5. Beach, R.: The management of ovarian tumors complicating pregnancy, labor, and the puerperium. Am. Jour. Obst., 1916, lxxiii, 1029–1041.
6. Bell, B.: The sex complex. New York, Wood, 1916. 232 pp.
7. Bensley, R. R.: Studies on the pancreas of the guinea-pig. Am. Jour. Anat., 1911–12, xii, 297–388.
8. Bensley, R. R.: The normal mode of secretion in the thyroid gland. Am. Jour. Anat., 1916, xix, 37–57.
9. Bond, C. J.: An inquiry into some points in uterine and ovarian physiology and pathology. Brit. Med. Jour., 1906, ii, 121–128.
10. Burnam, C. F.: Corpus luteum extract, with suggestions as to its use in gynecologic practice. Jour. Am. Med. Assn., 1912, lix, 698–703.
11. Carmichel, E. S., and Marshall, F. H.: The correlation of the ovarian and uterine functions. Proc. Roy. Soc., Lond., Series B, 1907, lxxix, 387–395.
12. Chalfant, S. A.: Subcutaneous transplantation of ovarian tissue, report of 32 cases with special reference to its effects on the menopause. Surg., Gynec. and Obst., 1915, xxi, 579–590.
13. Chappellier, A.: Follicles pluriovulaires et dégénérescence ovulaire chez la souris blanche. Compt. rend. Soc. de biol., 1909, lxvi, 543–545.
14. Chauffard, A., Laroche, G., and Grigaut, A.: Fonction cholestérinigénique du corps jaune. Compt. rend. Soc. de biol., 1912, lxxii, 223–225; 265–267.
15. Clark, J. G.: The origin, growth and fate of the corpus luteum. Johns Hopkins Hospital Reports, 1898–99, vii, 181–221.
16. Cohn, F.: Zur Histologie und Histogenese des Corpus luteum und des interstitiellen Ovarialgewebes. Arch. f. mikr. Anat., 1903, lxii, 745–772.

17. Corner, G. W.: The corpus luteum of pregnancy in swine. Carnegie Institution, Washington, Publication No. 222, 1915, pp. 69–94.
18. Culbertson, C.: A study of the menopause. Surg., Gynec. and Obst., 1916, xxiii, 667–685.
19. Daels, F.: On the relations between the ovaries and the uterus. Surg., Gynec. and Obst., 1908, vi, 153–160.
20. Dannreuther, W. T.: Corpus luteum organotherapy in clinical practice. Jour. Am. Med. Assn., 1914, lxii, 359–362.
21. De Lee, J. B.: Auto-transplantation of the corpus luteum. Surg., Gynec. and Obst., 1916, xxii, 228–231.
22. Fraenkel, L.: Die Function des Corpus luteum. Arch. f. Gynäk., 1903, lxviii, 438–545.
23. Frank, R. T., and Rosenbloom, J.: Physiologically active substances contained in the placenta and in the corpus luteum. Surg., Gynec. and Obst., 1915, xxi, 646–649.
24. Graves, W. P.: Influence of the ovary as an organ of internal secretion. Am. Jour. Obst., 1913, lxvii, 649–665; 779–785.
25. Hare, H. A.: Therapeutic application of ductless glands. Am. Jour. Obst., 1912, lxiv, 514–518.
26. Harrower, H. R.: Relation of the internal secretions to neurasthenia in women. Am. Jour. Obst., 1916, lxxiii, 630–637.
27. Heape, W.: The source of the stimulus which causes the development of the mammary gland and the secretion of milk. Am. Jour. Physiol., 1906, xxxiv, 499–500.
28. Hirst, J. C.: The control of disagreeable symptoms of the surgical menopause by the hypodermic intramuscular administration of corpus luteum extract. Am. Jour. Obst., 1916, lxxiii, 648–650.
29. Iscovesco, H.: Les lipoides de l'ovaire. Compt. rend. de la Soc. biol., 1912, lxxiii, 16–18, 189–191.
30. Jankowski, J.: Beitrag zur Entstehung des Corpus luteum der Säugetiere. Arch. f. mikr. Anat., lxiv, 361–389.
31. Lane-Claypon, J. E., and Starling, E. H.: An experimental inquiry into the factors which determine the growth and activity of the mammary glands. Proc. Roy. Soc. Lond., Series B, 1906, lxxvii, 505–523.
32. Lane-Claypon, J. E.: On the origin and life history of the interstitial cells of the ovary in the rabbit. Proc. Roy. Soc. Lond., Series B, 1906, lxxvii, 32–58.
33. Leighton, A. P.: The use of corpus luteum extract in the treatment of menopause disorders. Am. Jour. Obst., 1915, lxxii, 878–888.
34. Lewis, M. R., and Warren, H.: Mitachondria in tissue cultures. Am. Jour. Anat., 1914–15, xvii, 339–402.
35. Livon, J., Jr.: Sur l'action des extracts du corps jaune de l'ovaire. Compt. rend. Soc. de biol., 1909, lxvi, 549.
36. Loeb, L.: The formation of the corpus luteum in the guinea-pig. Jour. Am. Med. Assn., 1906, xlvi, 416–423.
37. Marshall, F. H. A.: The physiology of reproduction. Lond., Longmans, 1910.
38. Marshall, F. H., and Runciman, J. G.: On the ovarian factor concerned in the recurrence of the œstrous cycle. Jour. Physiol., 1915, xlix, 17–22.
39. Martin, F. H.: Ovarian transplantation. Surg., Gynec. and Obst., 1915, xx, 568–579.
40. Meyer, R.: Ueber Corpus-luteum-Bildung beim Menschen. Arch. f. Gynäk., 1911, xciii, 354–404.
41. Meyer, R.: Ueber die Beziehung der Eizelle und des befruchteten Eies zum Follikelapparat, sowie des Corpus luteum zur Menstruation. Arch. f. Gynäk., 1913, c, 1–19.
42. Miller, J. W.: Die Rückbildung des Corpus luteum. Arch. f. Gynäk., 1910, lxi, 263–286.
43. Miller, J. W.: Corpus luteum, Menstruation und Gravidität. Arch. f. Gynäk., 1914, ci, 568–619.
44. Mulon, P.: Sur l'existence de graisses antitoxiques. Compt. rend. Soc. biol., 1910, lxix, 389–391.
45. Niskoubina, N.: Sur la structure du corps jaune pendant et après la gestation. Compt. rend. Soc. biol., 1908, lxv, 767–769.
46. Parhon, C., Dumitresco, G., and Niseipesco, C.: Note sur les lipoides des ovaires. Compt. rend. Soc. biol., 1909, lxvi, 650–652.
47. Pearl, R., and Surface, F.: On the effect of corpus luteum substance upon ovulation in the fowl. Jour. Biol. Chem., 1914, xix, 263–274.

48. Regaud, C., and Dubreuil, G.: Sur les relations fonctionnells des corps jaunes avec
    l'uterus non gravide.
    1. État de la question et méthodes de recherchés.   Compt. rend. Soc. de biol.,
    1909, lxvi, 257–259.
    2. Statistiques de variations de volume de l'uterus par rapport a l'état des ovaires.
    Compt. rend. Soc. de biol., 1909, lxvi, 299–301.
    3. États successifs de l'uterus chez le même sujet aux diverses phases de la periode
    prégravidique.   Compt. rend. Soc. de biol., 1909, lxvi, 413–415.
49. Regaud, C., and Dubreuil, G.: Sur les follicules ovariens hémorrhagiques et sur le
    mécanisme de la déhiscense des follicules.   Compt. rend. Soc. de biol., 1909, lxvi,
    828–830.
50. Regaud, C., and Dubreuil, G.: Action du male sur le rut et l'ovulation chez la lapine.
    Le voisinage prolongé, sans accouplement, est insuffisant pour provoquer l'ovula-
    tion.   Compt. rend. Soc. de biol., 1908, lxv, 501–503.
51. Regaud, C., and Policard, A.: Fonction glandulaire de l'épithélium ovarique et de ses
    diverticules tubuliformes chez la chienne.   Compt. rend. Soc. de biol., 1901, liii,
    615–616.
52. Sobotta, J.: Ueber die Bildung des Corpus luteum bei der Maus.   Arch. f. mikr.
    Anat., 1896, xlvii, 261–309.
53. Sobotta, J.: Ueber die Bildung des Corpus luteum beim Kaninchen nebst einigen
    Bemerkungen über den sprungreifen Follikel und die Reihtungsspindeln des
    Kaninchens.   Anat. Hefte, 1897, viii, 469–521.
54. Sundwall, J.: The lachrymal gland.   Am. Jour. Anat., 1916, xx, 137–247.
55. Tuffier, T.: Transplantation of ovaries.   Surg., Gynec. and Obst., 1915, xx, 30–34.
56. Van der Stricht, O.: Sur le processus de l'excrétion des glandes endocrines; le corps
    jaune et la glande interstitielle de l'ovaire.   Archiv. Biol., 1912, xxvii, 585–722.
57. Vincent, S.: Internal secretion and the ductless glands.   Lond., Arnold, 1912.
58. Vineberg, H.: Fate of ovaries after hysterectomy.   Am. Jour. Obst., 1915, lxxii,
    144–147.

SURGICAL CONDITIONS COMPLICATING INTRA-UTERINE PREGNANCY*

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The diagnostician of surgical diseases is frequently confronted with the necessity of making a decision in regard to the advisability of operation for conditions complicating intra-uterine pregnancy. A question of possible or probable danger to two lives presents itself, and every effort must be made to save the mother and child. As Andrews says, the life of the woman is paramount, but both must be considered even at somewhat increased risk to the mother.

It is not often that normal pregnancy is complicated by surgical conditions. In the three years from 1914 to 1916 inclusive, there were more than 10,000 abdominal operations on women at the Mayo Clinic, and in that number 253 pregnant women were found to have definite surgical lesions not dependent on, although associated with, the pregnancy. One hundred and thirty-eight of these were advised to have operations and 123 were operated on. The case histories of twenty-three were not considered on account of lack of subsequent data confirming the diagnosis of pregnancy; thus 100 cases only are reviewed in part in this paper. Of this number, 16 women went to operation with pregnancy undiagnosed by the clinician. One of these had proceeded to a three months' gestation, but the remainder were mostly under two months and were diagnosed by the surgeon at the time of operation. This diagnosis was later substantiated by reports from the patients, except in three instances in which it was found to be erroneous.

During the same three-year period there were 130 pregnant women with surgical complications who did not come to operation. In this group are included only those cases in which the surgical pathology would warrant operation in the non-pregnant state. The surgical diagnosis was as follows:

PREGNANCIES WITH SURGICAL COMPLICATIONS—NON-OPERATIVE

SURGICAL DIAGNOSES

Appendicitis	31	Exophthalmic goiter	2
Adenoma of thyroid	31	Salpingitis	2
Cholecystitis	14	Uterus, prolapse of, cystocele	2
Fibroids	17	Cervical laceration	2
Gallstones	15	Cervical polyp	1
Varicose veins	5	Perineal relaxation	1
Ovarian tumor	1	Hodgkin's disease	1
Hemorrhoids	3	Gastric ulcer	1
Perineal laceration	3	Tuberculosis of spine	1
Adenoma of breast	2		

In 56 of this group the pregnancy was under three months, in 61 it was between three and five months, and in 13 it was more than five months. The 100 cases coming to operation have been listed according to surgical conditions found at operation:

PREGNANCIES WITH SURGICAL COMPLICATIONS—OPERATIVE

SURGICAL DIAGNOSES

Appendicitis	57	Pyonephrosis with stone	1
Cholecystitis and cholelithiasis	26	Ovarian and tubal abscess and stones in	
Fibroids	3	the common duct following cholecys-	
Adenoma of thyroid	4	tectomy	1
Exophthalmic goiter	4	Cyst of submaxillary gland	1
Tumor of breast	3	Laceration of the perineum	1
Hernia, inguinal	4	Abscess of the right cheek	1
Duodenal ulcer	2	Anal fistula	1
Salpingitis	2	Hemorrhoids	1
Exploration	2	Tumor of left antrum	1
Carcinoma of breast	2	Mixed tumor of the right parotid gland	1
Retroversion of the uterus	2	Osteomyelitis	1
Ventral hernia	1	Sterility (Pozzi operation)	1
Ovarian tumor	5	Epithelioma of arm	1

Appendicitis in pregnancy is a frequent occurrence and is most dreaded on account of its danger to mother and child. Paddock, quoting Schmidt in 1911, says that 2.5 per cent of women having appendicitis are pregnant, and 1 per cent of all pregnant women complain of or suffer from appendicitis. This percentage agrees with our statistics, that is, 57 (1.9 per cent) in pregnant women out of some 3000 cases of appendicitis in women operated on during the three-year period. The incidence of appendicitis is not higher during pregnancy than at other times, but a woman having had attacks of appendicitis is apt to have a lighting up of the condition during an ensuing pregnancy. De Lee asserts that this fact in itself should not necessarily indicate operation unless the patient's condition, or further attacks, make it advisable.

An acute attack of appendicitis during pregnancy calls more imperatively for operation than an attack during the non-pregnant state. The

danger of abortion or general peritonitis following ruptured appendix in these cases is greatly increased and the mortality rate is higher.   Murphy advised immediate operation, and quoted Wagner as estimating a 77 per cent mortality in the cases of acute appendicitis in which operation was not done.   Most of our cases (27) in which operation was done were of the interval type, and it is in this group, when immediate operation is not imperative, that decision is most difficult.

We have endeavored to determine the relative safety of the operation for both mother and child and the condition of the mother and child after delivery.   In the 100 cases there were 9 miscarriages, 2 of which were terminal events with the death of the patient from other causes. A conservative estimate would indicate that every fifth or sixth pregnancy in private practice ends in abortion (Williams).   It is of interest to note in our series that 1 miscarriage occurred after appendectomy for acute appendicitis, 1 after a gallbladder and appendix operation, 3 after single ovariectomy and appendectomy, 1 each after enucleation of a uterine fibroid tumor and thyroidectomy for simple goiter, and 2 (with death of the patient from peritonitis and pneumonia in 1 case and acute terminal nephritis and general peritonitis in the other) following gallbladder and appendix operations.   Four of the miscarriages occurred in gestations under two months, 2 at two months, 2 at three months, and 1 at four months.   Therefore, of the 50 patients operated on within a three months' gestation there were 7 (14 per cent) miscarriages; of 45 patients between three and five months, 2 (4.4 per cent) miscarriages. There were 5 pregnancies of more than six months in which there were no miscarriages.

The complication second in frequency to appendicitis is gallbladder trouble.   Of 2215 women having gallbladder operations during this period 26 (1.17 per cent) were pregnant.   The patient having cholecystitis or gallstones which are not producing dangerous symptoms should not be operated on during pregnancy.   In the 26 gallbladder operations in our series two patients died and one miscarried, a percentage which might not be so high in a larger group of cases.

Pelvic tumor is a very important surgical complication.   There were eight such, associated with pregnancy in the patients operated on, and 18 in the patients not operated on.   The decision of the operator in such instances will depend largely on the nature of the tumor.   Unless a fibroid tumor is in a position to obstruct at the time of delivery, or is producing dangerous symptoms, it should not be disturbed during preg-

nancy. If it is in a position to obstruct, a Cesarean section at term is probably the safest procedure.

Lockyer writes: "The indications for myomectomy on the gravid womb must be few, and this operation has been performed possibly more often than would be deemed justifiable." On the other hand, Davis, Kosmak, and others have reported successful operations followed by the delivery of normal children at term. Richardson stated that in his experience in every instance in which it seemed necessary to remove a fibroid from the pregnant uterus the operation was successful and the growth and birth of the child were not interfered with. Of the 20 patients with fibroid tumor and pregnancy examined in the Clinic during the three-year period, only three were operated on and one of these miscarried.

Ovarian tumor as a complication is considered with much graver concern. In such tumors trouble may occur by a twisting of the pedicle, causing rupture and producing abortion, or obstructing delivery. In 1916 Beach reviewed the subject exhaustively. He quoted from an article of Patton's published in 1906 in which 321 cases were reported. In 24 of these there was torsion of the pedicle, and of 95 patients treated expectantly there was a maternal mortality of 26.3 per cent against a mortality of 4.3 per cent in 184 patients operated on. The miscarriages were about equal—18.9 per cent in the former and 19 per cent in the latter. Barrett reported 38 patients not operated on before term, with a maternal mortality of 18.4 per cent as against 76 patients operated on with a maternal mortality of 2.6 per cent. In those treated expectantly there was 18 per cent of abortions and only 12.3 per cent in those operated on. Barrett advises early removal of the tumor because of the good results to both mother and child and the lessened danger at labor. He further states that even during the latter half of pregnancy the results are such as to warrant the removal. In eight of his cases of double ovariotomy six went to term. This would seem to disprove the idea that the internal secretion of the corpus luteum is necessary to the normal continuance of pregnancy.[7]

There were six ovarian tumors in our 253 cases. Five of these were operated on, a single ovary being removed in each case. In one other case an abscessed ovary and tube were removed. A miscarriage followed in this and in two other cases. In one case in which a diagnosis was made of pregnancy associated with a large uterine fibroid the patient was found to have an ovarian cyst at operation eight weeks after a normal delivery. Other operations were amputations of the breast,

nephrectomy (one), hemorrhoidectomies, partial thyroidectomies, and in one case an operation on the cervix.   This patient was sent in with a diagnosis of sterility, having had an apparently normal menstrual period three and one-half weeks before.   Notwithstanding a Pozzi operation, an early pregnancy was not interrupted and the patient went to a normal delivery.

Two radical breast amputations for carcinoma were performed, one at six and one-half months and another at seven months, without interruption of pregnancy.   In three other patients an adenoma was removed from the breast.   None of these miscarried.*

A nephrectomy for tuberculous kidney was performed without mishap.   Schmidt reviews Hartmann's 30 cases of nephrectomy and five additional from the literature.   There was a maternal mortality of two (5.7 per cent), known normal labor in 21, and death of the fetus in 15 per cent of the cases.   Harrigan and Beer each report a nephrectomy followed by normal labor at term.

Very rarely is a thyroid operation indicated during pregnancy.   Of 35 pregnant women with adenoma of the thyroid examined, 31 were advised to delay operation until after confinement.   Of 6 patients with exophthalmic goiters, 4 were operated on, but in one patient only was a primary thyroidectomy done.   The total number of women with exophthalmic goiters examined was 1055, of whom 6, or about ½ per cent, were pregnant.   Of the total number of 2404 women with simple goiters, only 35 (1.4 per cent) were pregnant.

Conclusions

1. Any operation which can be postponed until after confinement should not be done during pregnancy.

2. When necessary, operations for appendicitis can be done without undue risk to mother and child.

3. It is rarely necessary to operate for fibroid tumors complicating pregnancy, but when operation is necessary, it is associated with little danger.

4. The removal of an ovarian cyst during pregnancy is less dangerous to the mother than is expectant treatment.

5. While the time most favorable for operation is believed to be in the first half of pregnancy, when necessary, it can be done later.

* In a personal communication Speck reports the case of a woman three months pregnant who had her left breast accidentally shot away with a load of bird-shot. She went to normal confinement and was delivered of a normal living child.

REFERENCES

1. Andrews, E. W.: Diagnosis and management of acute extrapelvic conditions during pregnancy. Surg., Gynec. and Obst., 1916, xxiii, 657–659.
2. Barrett, C. W.: Ovarian tumors complicating pregnancy, delivery, and the puerperium. Surg., Gynec. and Obst., 1913, xvi, 28–33.
3. Beach, R. M.: The management of ovarian tumors complicating pregnancy, labor, and puerperium. Am. Jour. Obst., 1916, lxxiii, 1029–1041.
4. Beer, E.: Hypernephroma complicated by pregnancy; nephrectomy. Ann. Surg., 1916, lxiii, 630.
5. Davis, A. B.: Myomectomy at eighth week, pregnancy not interrupted. Normal delivery at term. Bull. Lying-In Hosp., 1913–1916, ix–x, 178–179.
6. De Lee, J. B.: Diagnosis and management of pregnancy in the presence of acute abdominal conditions. Surg., Gynec. and Obst., 1916, xxiii, 660–663.
7. Drips, D.: Studies on the ovary of the spermophile (spermophilus citellus tridecemlineatus), with special reference to the corpus luteum. Mayo Clinic Collected Papers, 1917, ix.
8. Harrigan, A. H.: Nephrectomy during pregnancy. Am. Jour. Obst., 1914, lxix, 500–501.
9. Kosmak, G. W.: Myomectomy during pregnancy. Am. Jour. Obst., 1916, lxxiii, 314–317.
10. Lockyer, C.: Multiple myomectomy in the sixth month of pregnancy; labour at term. Proc. Roy. Med., 1914, vii, part 2, 221–225.
11. Murphy, J. B.: Appendicitis in pregnancy—appendectomy. Clinics of J. B. Murphy, 1914, xxx, 1085–1097.
12. Paddock, C. E.: Pregnancy complicated by appendicitis. Am. Jour. Obst., 1914, lxviii, 401–419.
13. Patton, C. L.: Ovarian cysts situated above the superior pelvic strait, complicated by pregnancy. Surg., Gynec. and Obst., 1906, iii, 413–420.
14. Richardson, M. H.: Surgical diseases of the abdomen and uterus complicating pregnancy. Tr. Am. Surg. Assn., 1912, xxx, 608–616.
15. Schmidt, L. E.: Nephrectomy during pregnancy. Surg., Gynec. and Obst., 1915, xxi, 679–684.
16. Williams, J. W.: Obstetrics. N. Y., Appleton, 1903, 845 pp.

MYOMAS OF THE UTERUS, WITH SPECIAL REFER-
ENCE TO MYOMECTOMY*

W. J. MAYO

To my knowledge there has been no reported case of a tumor com-
posed of voluntary (striped) muscle-fibers of the fully developed type
found in voluntary muscle. It is true that rhabdomyomas occur,
especially in the genito-urinary tract, but the striped fibers are always
embryonic in character. True myomas are therefore of the involuntary
(non-striped) muscle, and wherever smooth muscle is to be found they
are an inherent possibility. Smooth muscle has a remarkable power
of hypertrophy, but this is not true of striated muscle, which reaches
its maximum in adult life and appears to be incapable of greater develop-
ment in later years.

Meltzer,[1] referring to Triepel's investigations, calls attention to the
fact that the permanent reserve power of the voluntary muscles is
comparatively small. Crile[2] and Cannon[3] have shown that under the
influence of fear or anger extraordinary reserve of the voluntary muscles
can be brought about temporarily. This, however, is not due to hyper-
trophy, but is the result of acceleration of the blood supply through
increased activity of the internal secretion of the thyroid, suprarenals,
and other endocrine glands, which at the same time inhibit gastro-
intestinal action through the autonomic system and reduce the circula-
tion of blood to the viscera. The increased muscular power comes about
in the same way in which an engine steaming at 190 pounds' pressure
would produce greater power than when steaming at 160 pounds'
pressure. Increased activity of the voluntary muscles results in fatigue,
owing to the acid products which accumulate, and these acids are re-
moved from the muscular system through bases which are quickly
supplied by food during rest. Stonewall Jackson, one of the greatest
soldiers America has produced, by taking advantage of this fact,—
dividing the march into periods with complete relaxation for a short

time between each period, and giving the soldiers, during this time of rest, such food as he could obtain,—was able to march infantry as many as 40 miles over bad roads in twenty-four hours. This obtained for them the unique appellation of "foot cavalry."

Smooth muscle, on the contrary, apparently cannot be speeded up to the same extent to meet emergencies, but must have time for muscle hypertrophy to take place. Muscle hypertrophies are work hypertrophies, such as occur from obstruction in the gastro-intestinal tract, or they depend on lack of proper stimulation, owing probably to failure of the nodal system, as shown by Keith,[4] which failure gives rise to such various conditions as cardiospasm, pylorospasm, stasis, Hirschsprung's disease, etc.

It has been shown by Cannon and Alvarez[5] that smooth muscle-fiber has within itself the power of contraction independent of nerve or blood supply. A bit of intestine placed in Locke's solution will beat for hours. Our knowledge of the heart is most complete in this detail; the heart-beat begins in the muscle-fibers of the auricle, and the impulses are collected in the sino-auricular node—a primitive muscle-nerve type of ganglion endowed with automatic function. These impulses are carried to the ventricle through the muscle bundle of His, timing the ventricular beat. All smooth muscle, as shown by Keith, has its primary contraction or its beat, so to speak. The intestinal tract has two beats: one from 15 to 20 times to the minute, which may act as the heart of the portal circulation (Mall), and the second, once or twice to the minute. The latter we recognize as peristalsis. The uterus has its beat, which, during pregnancy, becomes so marked that it is a diagnostic sign of value as the examiner places his hand over the suprapubic region to feel the uterine contractions.

As yet there has been no good explanation of the absence of myomas in the voluntary muscle and the frequency of these tumors in the involuntary muscle. The cause is undoubtedly connected with the primitive power of contraction of smooth-muscle fibers and their ability to hypertrophy quickly in response to demand. In this connection it is well to remember that the round, broad, ovarian, and uterosacral ligaments contain smooth muscle derived from the uterine wall, and that myomas and adenomyomas (Cullen[6]) may occur in these locations.

It has been shown that 12 per cent of white and 30 per cent of colored women of fifty years of age have uterine myomas. Clark and Miller[7] state that at the Charity Hospital in New Orleans 50 per cent of colored

women of thirty-five who have not borne children have myomas of the uterus. This high percentage indicates that only a small proportion of women with myomas have symptoms, and, therefore, we cannot accept the opinion, so frequently expressed, that every myomatous uterus should be considered surgical. We should believe, rather, that only those myomas which are giving rise to symptoms require operation, although all women who have myomas should be examined at intervals to see that the tumors are causing no harm. It has been estimated that 30 per cent of women with myomas die within five years if not operated on. Noble,[3] as a result of his investigation of 2274 cases in which myomas were removed by hysterectomy, states that in 30 per cent there were pathologic conditions present which would have led to death. We can accept these figures if the premise be changed; that is, that the lives of 30 per cent of women who have myomas which cause symptoms would be materially shortened if the myomas were not removed. Thus we exclude that large number of women who have small myomas which are not producing symptoms.

The most common conditions indicating operation are those which result from: (*a*) hemorrhage; (*b*) degeneration of the tumor (22 per cent); (*c*) malignant disease, usually carcinoma of the body of the uterus (4 per cent); 10 per cent of women more than fifty years of age who come to operation for uterine myoma have complicating malignancy; (*d*) tumors causing pressure. The large majority of patients with tumors which can be felt suprapubically belong to this group, and, with or without symptoms, should be operated on. In 30 per cent of patients with myomatous uteri causing symptoms the ovaries and tubes are so seriously diseased as to require operation independently of the myomas.

The diagnosis of uterine myomas in about 5 per cent of our cases was more or less incorrect. The presence of a tumor of the ovary, either benign or malignant, usually caused the failure of differentiation, especially when small fibroid nodules, of no consequence in themselves, were to be felt in the uterus.

The use of the roentgen ray and radium in disease is interesting and in some respects encouraging. It seems to be generally agreed that the gamma rays are the responsible agents, and that there is little difference in effect whether they are produced by radium or the roentgen ray. Radium has the advantage of containing definite and measurable quantities. It is portable and convenient, and does not require great

skill in application.   The roentgen ray requires greater skill, and should
be used only by the more expert.   The treatment of uterine myomas
by irradiation would appear to be contraindicated in degenerating
and submucous tumors, where inflammatory disease of the ovaries
and tubes co-exist, and in all doubtful tumors.   Forssell,[9] the lead-
ing Scandinavian roentgenologist, states that he caused the disap-
pearance of 30 per cent of sarcomas; but he has had no four-year
cures.   He further states that he has many cures of superficial carcino-
mas, but few of deep-seated carcinomas.   Holding, of the Memorial
Cancer Institute of Cornell, agrees with these statements and adds much
to our knowledge of the subject.   He calls attention to the fact that
irradiation has an especially destructive effect on nuclei, and the greater
the nucleation of the growth, the better the effect of irradiation.   He
states also that irradiation will often cause healing over a cancerous
surface and give a fictitious appearance of cure.   Colwell and Russ[10]
show that irradiation acts markedly to obliterate the capillaries, perhaps
because they have only the inner endothelial coat.   It does not act to a
great extent on the larger three-coated blood-vessels.   This peculiarity
accounts for the splendid results obtained by irradiation in vascular
and lymph tumors, and also for the extraordinary reduction of the
enlarged leukemic spleen.   The splenic vessels have only the inner coat.
Colwell and Russ, however, show that islands of cancerous tissue cling
to the larger vessels where irradiation will seldom destroy them.   Cer-
tainly one would hesitate to trust to irradiation for the cure of a probably
malignant change in a myomatous uterus.   Our own experience in this
connection is too limited to be of value, although in the modest number
of cases of all sorts in which we have used these agents during the past
seven years we have had a few excellent results, but unfortunately only
a few in malignant disease, excepting superficial lesions.

One cannot escape from the conviction that in myomatous disease
the use of radio-active substances is destructive—non-operative, but not
conservative.   In the great majority, if not all, of the cases in which the
myomas completely disappear under their use, the patient loses the
function of the ovaries, tubes, and uterus, although the non-functionat-
ing remnants were left in situ.

It is urged by those who are devoted to the radio-active treatment
of myomas that many patients are such poor surgical risks that they
cannot be operated on, and for that reason there is a wide field of useful-
ness for these agents.   We are told that certain patients cannot be

operated on because of marked secondary anemia, yet I have operated many times when the hemoglobin was under 30 and twice when it was under 20, with recovery of the patients. In any event the condition of such patients can be improved by blood transfusion, for the practical benefits of which we are indebted to Crile. Again, we are told that certain patients cannot be operated on because of high blood-pressure; but unless the high blood-pressure is due to cardiorenal or thyroid disease, it does not apparently add to the operative risk. We frequently operate on patients of the uncomplicated arteriosclerotic type with blood-pressure from 180 to 250 or more, and we have never had a death following the operation which we could attribute to the hypertension.

Uterine myomas are rather frequently associated with goiter. The estimation of the operative risk depends on the condition of the thyroid (goiter heart). Heart lesions of any description lead to a fear of operation. The common type of lesion is mitral, beginning in the young, especially females, as an endocarditis in connection with chorea, or "inflammatory rheumatism," and without hypertension. If well compensated, this type of lesion apparently does not increase the surgical risk. Women with bleeding submucous myomas occasionally develop heart lesions of the same character, with marked secondary anemia, probably due to a similar infection, and the condition is an indication for, rather than against, operation.

Hysterectomy has been and still is the operation of choice for all symptom-producing myomas, and it has much to commend it. In patients above forty years of age, and especially those with degeneration of the tumor, this operation is indicated. Supravaginal hysterectomy has a definite technic which has been so thoroughly and carefully worked out in the past twenty years that it has become the standard operation. Preserving the cervix renders the operation easier and safer, but the cervical remnant has no function and two unfortunate propensities: First, it leaves the patient with a liability to cancer—an average liability, according to our experience, although Winter and others believe that in myomatous disease the liability is increased—and, second, it is the cause of the large majority of those sometimes troublesome vaginal discharges which go by the name of leukorrhea, due to subsequent disease of the mucous glands of the cervix. For this reason, in all cases of erosion, cystic degeneration or other disease of the cervix, we remove the cervix with the body of the uterus, provided it can be done without unduly increasing the risk of the operation.

There has been a great deal of difference of opinion as to whether or

not the ovaries should be saved. It would seem, however, that to remove the normal ovaries merely because we are doing a hysterectomy is an unwarranted mutilation. Norris and Clark's[11] investigations show that saving the ovaries materially reduces the unpleasant physical and nervous effects which often follow hysterectomy. That the ovaries have an internal secretion as well as the function of ovulation is well known, and in the young this internal secretion, even from ovaries in which the function of ovulation never occurs, causes at least development of the feminine characteristics.

The internal secretion of the ovary and testicle also has to do with the closure of the epiphyseal lines in adolescence; and removal of these organs in the young leads to late closure of the epiphyseal lines and increased growth of the long bones, which, in connection with a hyperactive pituitary secretion, produce the tall, spindle type of giantism. That the function of the ovaries is entirely independent of nerve supply is shown by the experience of Tuffier,[12] who, in operating for pus tubes, removes the ovaries and tubes, sterilizes the ovary either by passing it through an alcohol flame or by dipping it in tincture of iodin, and implants it in the abdominal wound just outside the peritoneum. For a few months after operation the patient shows marked evidence of beginning menopause; in from four to six months these symptoms disappear, and menstruation reappears and continues in a normal manner. Only autografts, however, have this property; in Tuffier's experience homografting and heterografting of ovaries were a failure. Beatson,[13] of Glasgow, found that in some hopeless cancers of the breast removal of the ovaries produced an extraordinary effect on the cancer, several patients of this description being apparently cured. Beatson is a most distinguished as well as conservative surgeon, and his results, which have been duplicated by others, well show the remarkable effect of stopping the internal secretion of the ovaries.

We have been able to save one ovary in more than 50 per cent, and both ovaries in more than 25 per cent, of all the hysterectomies we have done for myomatous disease. From the standpoint of conservation of the ovary, hysterectomy is preferable to radium and the roentgen ray, since when thus effectively treated the ovaries are destroyed. Acknowledging, as we must, the great benefits which have accrued to woman through hysterectomy, we cannot blind ourselves to those physical and nervous changes which sometimes follow, especially in younger women. It would be interesting to know what percentage of divorces have had their origin in this operation. It is not that hysterectomized women

become coarse, although they often gain in weight, but certain physical and nervous changes take place which may result in unhappiness. The noblest instinct of woman, that of motherhood, is at hazard. Because of the ease and the surgical certainty of hysterectomy, have we not sometimes too quickly advised and practised a mutilating operation? I regret to say that we now occasionally see a young woman in whom a condition equivalent to hysterectomy with removal of both ovaries has been brought about by radium or the roentgen ray. To one who takes a view of the whole situation, myomectomy must present itself as the only truly conservative procedure, and becomes the operation of choice for a large number of patients, provided always it can be done without an increase of risk and with reasonable certainty as to cure.

Myomectomy for myomas of the uterus has not been a popular operation. It has been urged against it, first, that the mortality of the procedure itself is higher than that of hysterectomy, and, second, that more tumors would develop and necessitate hysterectomy later. As to the mortality: From January 1, 1891, to September 1, 1916, we have done 504 consecutive myomectomies with four deaths in the hospital—a mortality of 0.8 per cent. Counting as a death from the operation every patient who died in the hospital following myomectomy, without regard to cause or length of time after operation, certainly this mortality compares favorably with that of hysterectomy. As to the second objection, only five patients required hysterectomy later for any cause.

It must be taken into consideration, however, that the patients whom we subjected to myomectomy were in a way selected cases. Myomectomy was not often done in those over forty, and it was not frequently done after the age of thirty-five unless the conditions were such as to make it safe. On the contrary, it was done for the majority of patients with myomas who were under thirty-five years of age, and for practically all under thirty years. As the tumors which require operation are much more frequent after the fortieth year, it can be readily seen that we have been conservative in choosing cases for myomectomy.

Myomectomy is a more difficult operation than hysterectomy, because the technic must be varied according to the character, situation, size, and number of tumors. But myomectomy does not present greater difficulties than can be easily mastered by the experienced surgeon. I have previously described[14] the technic of this operation, and have found it necessary to make but little change since.

Fourteen patients were pregnant at the time the myomectomy was
'17—20

performed, and the majority went to term and were delivered of living children.   When it is considered that in the latter group the tumors were degenerating with acute symptoms, and that in a large proportion indications of spontaneous emptying of the uterus were present at the time of the operation, it is remarkable that the disturbance so frequently quieted down without premature expulsion of the child.   In not a single instance have we been obliged to do hysterectomy on the pregnant myomatous uterus with a non-viable child.

Twenty-four of our 504 myomectomized patients have had living children since the operation, and seven have had two or more.   Thirty-eight living children to date following myomectomy is a strong argument for the conservative operation.   Five others are normally pregnant now.

From this investigation as to actual results covering a period of twenty-five years it is evident that the operation of myomectomy has not received the attention it merits.   We should bend every effort to improve the technic and further the indications for this operation, the only truly conservative procedure for myomas of the uterus, an operation which removes the tumor and leaves the patient as she would have been had she never possessed it.

REFERENCES

1. Meltzer, S. J.: The factors of safety in animal structure and animal economy. Harvey Lectures, 1916–1917, ii, 139–169.
2. Crile, G. W.: Acidosis and its dominating influence in surgery. Tr. Am. Surg. Assn., 1915, xxxiii, 419–429.
3. Cannon, W. B.: Some relations between emotions and glands of internal secretion. Journal-Lancet, 1916, xxxvi, 685–688.
4. Keith, A.: A new theory of the causation of enterostasis.   Lancet, 1915, ii, 371–375.
5. Alvarez, W. C.: The motor functions of the intestine from a new point of view. Jour. Am. Med. Assn., 1915, lxv, 388–394.
6. Cullen, T. S.: Adenomyoma of the round ligament and incarcerated omentum in an inguinal hernia, together forming one tumor. Surg., Gynec. and Obst., 1916, xxii, 258–260.
7. Clark and Miller: Personal communication to the author.
8. Noble, C. P.: Fibroid tumors of the uterus: A study of the degenerations and complications in 2,274 consecutive cases; including 337 cases of the writer's; also a study of 4,880 consecutive cases in their relation to carcinoma and sarcoma of the uterus. Jour. Obst. and Gynec., Brit. Emp., 1906, x, 436–477; Jour. Am. Med. Assn., 1906, xlvii, 1881–1886.
9. Forssell: Personal communication to the author.
10. Colwell, H. A., and Russ, S.: The effects of x-rays upon various organic substances. Arch. Middlesex Hosp., London, 1911, xxvii, 63–70.
11. Clark, J. G., and Norris, C. C.: Conservative surgery of the pelvic organs in cases of pelvic peritonitis and of uterine myomas, with the review of the immediate and after-results of 299 cases.   Surg., Gynec. and Obst., 1910, xi, 398–413.
12. Tuffier: Personal observation, Mayo, W. J.: A visit to some of the hospitals and surgical clinics of France.   Northwest. Lancet, 1911, xxxi, 405–411.
13. Beatson, G. T.: On the treatment of inoperable cases of carcinoma of the mamma, suggestions for a new method of treatment, with illustrative cases. Lancet, ii, 1896, 104–107; 162–165.
14. Mayo, W. J.: Some observations on the operation of abdominal myomectomy for myomas of the uterus. Surg., Gynec. and Obst., 1911, xii, 97–102.

DUCTLESS GLANDS

THE THYROID HORMONE *

E. C. KENDALL

Enzymes are known only by the products of their activity. The same may be said of the thyroid, with this distinction, that no chemical substance has ever been shown to be the direct product of thyroid activity, and the only end-results we can now recognize are clinical and experimental conditions of man and animals. Surgeons, clinicians, pathologists, physiologists, and chemists have contributed to a voluminous literature concerning this gland, but its function has not been revealed. Clinicians have failed to agree concerning thyroid disturbances, pathologists have still to come to an understanding in regard to the histologic pictures of disturbed thyroid activity, physiologists have not yet concurred in what is the function of the gland, nor has any physiologic test of its activity been universally accepted.

The clinician is able, by an analysis extending over thousands of cases and many years' observation, to establish certain fundamental aspects of thyroid activity which find their proof in definite clinical syndromes. The pathologist can relate conditions of the gland showing various stages of activity and inactivity to certain clinical manifestations. The physiologist is able to assign, within broad limits, the function of the thyroid, but no ultimate proof or quantitative conception could be evolved until the thyroid hormone was separated as a chemical entity and its chemical identification made certain. With the structural formula of the hormone established, its mode of action may be directly attacked and the final proof of the function of the thyroid becomes a possibility. The circle may be completed and thyroid activity measured, not by the clinical results of its action alone, but also by definite chemical substances which will be shown to be the end-products of its activity.

The record of the chemical study of the thyroid is possibly the most unsatisfactory of all the different phases of the investigation of the gland. Twenty-one years previous to this writing Baumann reported the pres-

ence of iodin as a normal constituent of the thyroid. He did not separate the iodin-containing compound, and although several other attempts have been made, up to the time of the present investigation no single crystalline substance of any kind has been separated from the thyroid, which possesses physiologic activity the same as desiccated thyroid.*

As a result of the physiologic investigation of the thyroid, more and more importance has been attached to the presence of iodin in thyroid split products, and experiments with the entire glandular substance have established the necessity for the iodin compound of the thyroid in order to produce typical thyroid activity.[8,10,15] It was recognized that the iodin compound in the thyroid is of a different nature than any other known iodin compound. Several iodin compounds have been tried to see if, by chance, they did possess physiologic activity similar to desiccated thyroid, but none has been found.[13]

Desiccated thyroid possesses certain definite physiologic activity. By a separation of the thyroid proteins based on solubilities Oswald showed that thyreoglobulin[16,17] still possessed the physiologic activity of desiccated thyroid. However, a chemical hydrolysis of the proteins of the thyroid with sulphuric acid destroys the physiologic activity of the gland. Of recent years Baumann's iodothyrin, prepared by acid hydrolysis, has been more and more discredited,[17] and at the present time it is not regarded as possessing pharmacologic properties the same as desiccated thyroid. Since it had been shown that desiccated thyroid and the separated protein thyreoglobulin both possess definite physiologic activity, the present investigation was undertaken with the hope that the thyroid proteins could be broken down by some method other than an acid hydrolysis, which would not destroy the physiologic activity of the thyroid hormone.

The Investigation of the Chemical Constituents of the Gland, with Isolation of the Iodin-containing Compound in Pure Crystalline Form.— I began the chemical investigation of the thyroid in September, 1910, and have continued it practically without interruption up to the present time.

Starting with fresh and desiccated thyroid the present investigation was at first concerned with the diffusibility of the iodin-containing compound. Iodin is not dialyzable from the thyroid proteins, and it will withstand rather severe chemical treatment and still be undialyzable

* The definition of typical thyroid activity used throughout this paper is given on page 335.

through a collodion sack in running water. In order to determine the stability of the iodin compound, various hydrolytic processes were applied to the thyroid proteins. Among others the alcoholic alkaline hydrolysis used by Vaughan[24] was tried, and, with some slight modifications, was found to produce a deep-seated hydrolysis without breaking off iodin from its organic combination. Furthermore, the hydrolysis so alters the iodin-containing compounds that about 70 per cent of the total iodin is dialyzable. Another change brought about by the hydrolysis is the solubility of the iodin compounds in acid. About 50 per cent of the total iodin contained in the hydrolyzed products is soluble in acids, and 50 per cent is insoluble. The iodin in the acid-insoluble portion is to a large extent not dialyzable. The presence of iodin in organic combination and in non-dialyzable form was encouraging evidence of the stability of the iodin compound, and invited further investigation.

The physical and chemical properties of the acid-insoluble group of hydrolyzed constituents will be described somewhat in detail, since this will bring out the chemical problems involved and some of the difficulties encountered.

An alkaline solution of the acid-insoluble constituents is dark brown, almost black, with a green fluorescence, and shows a Tyndal phenomenon with a beam of light. The non-diffusibility, fluorescence, and Tyndal phenomenon show that we are dealing with a solution of colloidal nature. Among the acid-insoluble constituents are fatty acids resulting from the original fat in the desiccated thyroid, and sulphur, which results from the decomposition of cystin. The solution has no characteristic odor other than a general fatty smell. The first step used in the method of separating the iodin compound is to dry the acid-insoluble constituents, mix with infusorial earth, and extract with petroleum ether to remove fatty acids and sulphur.

The solubility of the iodin compound in organic solvents varies, depending on the solvent used, the presence of water, whether acid is present, and the temperature. About 10 per cent of the total iodin is soluble in ethyl ether, but only a small amount is soluble in petroleum ether. After the removal of the fat and sulphur the powder is dissolved in sodium hydroxid, filtered free from infusorial earth, and is again acidified. This precipitate is heavy, flocculent, and amorphous, and when heated above 40 to 50 C. in aqueous solution, turns to a black, tarry mass. On cooling and drying it is found to be brittle and may be broken up into a fine, dry powder almost black. The dry powder is soluble in

acid ethyl alcohol and aqueous solutions of sodium, potassium, and am-
monium hydroxids and carbonates. It is in part precipitated from acid
alcohol by the addition of sodium carbonate, the portion precipitated
being a sticky, black, tarry mass. Most of the iodin-containing com-
pounds are soluble in alcohol in the presence of sodium carbonate, so
that this is a valuable aid in the gross separation of the black, tarry im-
purities from the constituents which contain iodin. However, some of
the iodin is carried down by the sodium carbonate precipitation, showing
that the iodin compound, although probably the same throughout all
the different precipitates, is attached to various groups of compounds
which possess different solubilities.

If barium hydroxid is added to the alcohol solution after removal of
the sodium carbonate precipitate, practically all the rest of the dark-
colored compounds are precipitated by the barium. This precipitate
carries down approximately 50 per cent of the iodin present. This is
still another evidence of the different groups to which the iodin com-
pound is attached. Since the alcohol solution remaining after precipita-
tion with barium is light straw-colored, the alcohol-barium-soluble con-
stituents to which the iodin compound is attached are almost colorless.

Similar separations can be produced in aqueous solution. If the
dark-brown alkaline solution of the hydrolyzed products is acidified,
almost all the color and iodin compounds are thrown out of solution.
Barium, calcium, and magnesium salts, added to an alkaline aqueous
solution of the acid-insoluble hydrolysis constituents, precipitates prac-
tically all the dark-colored compounds, leaving a very light-colored solu-
tion. This precipitation divides the iodin present. About one-half is
precipitated by the alkaline earths and one-half is soluble.

These precipitation and solubility properties clearly show the nature
of the material with which one has to work. It is a mixture of com-
pounds in colloidal form. The problem is not one of separating a mechan-
ical mixture alone, but as none of these products contain more than 5
to 10 per cent of iodin, it is apparent that further hydrolysis must be
employed to break the bond linking the iodin compound with its heavy
colloidal components.

The most striking property of the acid-insoluble group of hydrolyzed
products is their acidic nature. They can be dissolved in alkali and re-
precipitated by acid without appreciable loss of iodin.

Many attempts were made to separate the iodin compound by its
solubility and precipitation properties with various reagents. No spe-

cific precipitant was found. No difference in solubility was found which could be used to effect a separation. After many attempts to separate the iodin compound had failed, it became apparent that the compound was not present in free form, but was still firmly bound to some unknown substances.

Experiments showed that iodin was not broken off when dissolved in moderately strong sodium hydroxid. In the hope that heating in aqueous sodium hydroxid might produce a further hydrolysis, the acid-insoluble constituents of the alkaline-alcoholic hydrolysis were heated several hours in 5 per cent sodium hydroxid. It was then found that treatment with sodium hydroxid, followed by precipitation with an acid, will not effect a separation of the iodin compound from the black colloidal impurities. There is no indication that sodium hydroxid breaks the bond between the iodin compound and the impurities, at least in such a manner that it cannot be readily reëstablished. The solubility of the compounds present, which do not contain iodin, closely parallels the solubility of the iodin-containing compound, and, as far as alkali and acid are concerned, no appreciable separation can be brought about by alternate treatment with each.

Since the addition of a soluble barium salt to an alkaline solution of the acid-insoluble products of hydrolysis precipitates practically all the brown impurities and does not carry down all the iodin, this separation was investigated to see whether the percentage of iodin in the acid-insoluble constituents could thereby be increased. The acid-insoluble constituents were dissolved in dilute sodium hydroxid and barium hydroxid was added. The solution was heated in a nickel crucible at 100 C. for eighteen hours. This treatment produced a precipitation of the brown compounds, giving a light-yellow filtrate of the barium-soluble constituents. Determination of the iodin content of the filtrate showed that about 50 per cent of the iodin present had been precipitated from the alkaline solution by barium hydroxid and 50 per cent remained soluble. Sodium sulphate was added to the water solution containing the barium-soluble constituents, and the barium was removed as sulphate. The solution was then acidified, and a copious precipitate obtained which still retained iodin. The precipitate was filtered off and dried. Analysis showed that the percentage of iodin had been very materially increased by this treatment. The percentage of the iodin in the starting material was about 5 per cent. After treatment with barium, as outlined above, and reprecipitation with an acid, the iodin was found to be about 15 per cent.

The portion of the starting material which had formed a dark, floccu-
lent precipitate with barium hydroxid, was dissolved in sodium hydroxid
and sodium sulphate. The barium sulphate was removed, and the solu-
tion was acidified. A precipitate formed on the addition of the acid, and
when this was filtered off and dried, it too was found to contain an in-
creased percentage of iodin. By treatment with barium hydroxid the
percentage of iodin contained in the hydrolyzed constituents of the thy-
roid proteins had been increased.

The question arose, How far could this treatment be carried out as a
method of purification? The two precipitates were dissolved in separate
solutions of sodium hydroxid, barium hydroxid was added to each, and
the solutions were heated in nickel crucibles for eighteen hours at 100 C.
The insoluble portions were filtered off, the barium was removed as out-
lined above, the barium-soluble constituents of each crucible were com-
bined and again acidified, the precipitate filtered off and dried, and analy-
sis showed that the percentage of iodin present had increased in the
barium-soluble portion to 26 per cent. With many misgivings the pre-
cipitation with barium and heating in a nickel crucible were repeated
still another time. The percentage of iodin in the precipitate obtained
was 33 per cent. Still another treatment yielded a product containing
42 per cent of iodin. The amount of material now consisted of less than
200 mg. The success of the method, however, called for still further
treatment. It was carried out in the same manner, and a precipitate
containing 47.3 per cent of iodin was obtained. The character of the
precipitate had changed and the color of the solutions had almost dis-
appeared. It seemed probable that some other method of purification
could now be applied to the preparation containing 47.3 per cent iodin.

The material was dissolved in 95 per cent alcohol; solution was com-
plete. The alcohol was evaporated on a water-bath to a small volume,
in the hope that some crystals might separate. By a chance, however,
the dish containing the alcohol evaporated to dryness, and the dried
precipitate was heated for about an hour after the alcohol had been
driven off. It was thought that on the addition of more alcohol the
white powder on the bottom of the dish would again be dissolved, and,
possibly, crystals might still separate. More alcohol was therefore
added, but a white incrustation on the bottom of the dish was insoluble
in alcohol. I believed that this treatment had effected a further sepa-
ration, that the iodin-containing compound was redissolved in the al-
cohol, and that the white incrustation represented impurities. It was
filtered off. The weight of this white powder was 18.6 mg. It was

dissolved in sodium hydroxid and a portion of it was used to determine iodin, when it was found that the iodin amounted to 60 per cent. The white incrustation was, therefore, not an impurity, but the iodin compound itself. Its solubility in alcohol had been changed by heating the residue left after evaporation of the alcohol. More of the acid-insoluble constituents resulting from hydrolysis of the thyroid proteins were treated in precisely the same manner, and about 200 mg. of the white residue were obtained. When this was dissolved in aqueous sodium hydroxid, precipitated by adding sulphuric acid and boiling, it was converted into fine white microscopic crystals. For reasons which will be given hereinafter this iodin compound has been named "thyroxin," and it will be referred to by that name throughout the remainder of this article.

As the yield of thyroxin depended on the amount of desiccated thyroid which could be treated at any one time, it was decided to enlarge our facilities for the hydrolysis of desiccated thyroid, which, up to this time, had been carried out in glass flasks. An 11-gallon galvanized-iron tank was constructed, which could take care of 500 grams of desiccated thyroid at one time. The acid-insoluble constituents were obtained as before. These were dissolved in dilute sodium hydroxid, barium hydroxid was added, and the steps outlined above were carried out. No crystals of thyroxin were obtained.

The work from this point will be presented in a logical, rather than a chronologic, order, as many months were spent in elucidating the factors which prevented the isolation of more crystals.

After working for fourteen months in an endeavor to repeat the first isolation of the crystals it was found that there were five conditions which must be fulfilled before the compound could be isolated in pure crystalline form. These are:

1. *The effect of temperature on the precipitation with an acid.*—When the partially purified, iodin-containing constituents are precipitated by an acid, the precipitate is flocculent and amorphous. If this is heated to 40 or 50 C., it assumes a fine, granular form which can be filtered and washed very readily. This procedure was followed because of the facility of handling the precipitate. Warming of the acid solution does not break off any iodin in inorganic form. If, however, this precipitate, which was prepared by warming the solution after the addition of the acid, is dissolved in alkali and heated with barium hydroxid, and the solution is again acidified, some iodin in the inorganic form may be found in the solution. If the precipitation by an acid is carried out in the cold,

subsequent heating with barium hydroxid and reprecipitation does not break iodin off in the inorganic form.

As only one stage of this treatment could be carried out in one day, twenty-four hours intervened between the first acidification and warming of the solution and the second precipitation, after which iodin was demonstrated in the inorganic form in the filtrate. This time interval formed a convenient screen behind which the deleterious action of heat remained hidden for many months. This influence of temperature on acidification was one of the most important causes for the failure to separate more crystals. Fearing that a concentrated sodium hydroxid solution would destroy the iodin compound, we had been neutralizing the alkali which was used to effect the primary hydrolysis with sulphuric acid before evaporating off the alcohol. As the amount of free alkali remaining in the alcohol was variable, depending on the amount of ammonia which had been evolved and the amount of water and carbonate in the alkali, it frequently happened that a slight excess of acid was added, so that the alcohol was evaporated off in the presence of a small amount of acid. This, we finally showed, has a very destructive action on partially purified thyroxin. In this connection it seems probable that the lack of physiologic activity of iodothyrin is explained by this action of acid on the iodin-containing compound. The iodin may not be broken off by treatment with acid, but the chemical properties, and undoubtedly the structural formula of the nucleus to which the iodin is attached, are so altered that the compound loses its physiologic activity. This action is discussed on page 334.

2. *The effect of heating the alkaline hydrolysis solution in the presence of metal.*—At first the hydrolysis was carried out in glass flasks. When an 11-gallon galvanized-iron tank was substituted, the hydrolysis was carried out apparently just the same, but it was found that with the metal the hydrolysis in an alkaline solution resulted in the breaking off of the iodin in the inorganic form. Investigation showed that in alkaline solution, iron, zinc, copper, tin, lead, German silver, and, in fact, all metals except nickel and the heavy metals, gold, silver, and platinum, break iodin off from its organic combination. A heavily enameled cast-iron kettle was found to give a satisfactory surface for a container in which to carry out the primary hydrolysis with sodium hydroxid in alcohol. Later this was replaced by a nickel kettle.

3. *The effect of carbon dioxid.*—During the first separation of crystals carbon dioxid was neither employed directly nor was its effect excluded from the various steps in the process. After many months of failure to

separate more of the iodin compound in crystalline form it was found that carbon dioxid plays an important rôle in the separation of thyroxin from the impurities. By chance an alkaline solution containing a partially purified preparation of thyroxin mixed with a large amount of impuri-- ties was precipitated with carbon dioxid instead of sulphuric acid. The precipitate was filtered on a Buchner funnel and washed with distilled water. Instead of the distilled water running through lighter colored than the first filtrate, it was almost black. Investigation showed that the black impurities were insoluble in water saturated with carbon dioxid, but that they were soluble in distilled water. Further investigation showed that there was some unexplained action of carbon dioxid on thyroxin when certain impurities were present which permitted its being separated in the crystalline form. Even after this reaction was dis- covered its explanation was, for many months, obscure. It will be dis- cussed hereinafter under the properties of thyroxin (p. 328).

4. *The effect of temperature during the treatment of a solution with car- bon dioxid.*—After it was found that carbon dioxid had a very important action which allowed thyroxin to be isolated in crystalline form, carbon dioxid was added to the various solutions, first in the cold, and then it was added to the solutions warmed to various temperatures up to 100 C. It was found that with the preparations which were contaminated with a large amount of impurities, the passing of carbon dioxid into a solution above 50° to 60° C. resulted in breaking off iodin. This was confirmed many times, and, while for a long time unexplained, I found that it was a condition which had to be controlled so that when the solutions were treated with carbon dioxid it was always done in the presence of an iced solution.

5. *The effect of different samples of desiccated thyroid.*—The fifth point is one beyond control, and was found to rest on the condition of the desiccated thyroid employed. Rarely do two samples of desiccated thyroid respond the same to the alkaline alcoholic hydrolysis. It ap- pears probable that bacterial or other decomposition so alters the pro- teins in some samples that it is impossible to separate any of the iodin compound.

These five factors finally became apparent after a consideration of all the results obtained over a course of two years' investigation. The most important cause for the confusing conditions found during the separation is the fact that the progressive purification of the iodin com- pound changes its properties. The chemical properties of thyroxin are completely masked during the early stages of purification by the impuri-

ties which are present. Barium so affects the impurities that their solubilities in acid and alkali are altered sufficiently to allow of a separation of the iodin compound. Barium apparently does three things: It produces some degree of hydrolysis and destruction of some of the impurities; it forms a precipitate with some of the impurities which is insoluble in sodium hydroxid, and it also carries down mechanically certain of the · colloidal impurities when it is precipitated by sodium sulphate. Very little of the iodin-containing compounds are carried down mechanically with barium sulphate. The solubility of thyroxin with barium was for a long time very confusing, but it was finally found to be as follows: If barium hydroxid is added to a solution of pure thyroxin dissolved in sodium hydroxid, an insoluble barium salt is formed which is very insoluble in sodium hydroxid. If barium hydroxid is added to a suspension of thyroxin which had been precipitated from an alkaline solution by an acid, then barium hydroxid does not form a barium-insoluble salt, and although the solution is alkaline, thyroxin is neither dissolved nor made insoluble. The mixture may be boiled and filtered, and if the residue is then treated with a solution of dilute sodium hydroxid, thyroxin is dissolved.

Some of the chemical properties changing with progressive purification are as follows: Carbon dioxid and hydrochloric acid both will break off iodin from a partially purified preparation, but after thyroxin has been separated in pure form, they have no such action. The solubility of thyroxin in barium hydroxid is paradoxical at different stages of the purification. Partially purified thyroxin is soluble in sodium carbonate and in alcohol. Pure thyroxin is insoluble in both. These paradoxical aspects can now be explained by the effect of the impurities reacting with thyroxin. The impurities attack certain groups of thyroxin which will be discussed on page 327. It is remarkable that all these factors were unconsciously controlled during the first purification, especially as it took many months to find out that there were so many separate and distinct influences at work causing the destruction of the compound.

After many months of trial these five factors were all controlled, and a method based on our knowledge of the physical and chemical reactions of thyroxin was evolved which can now be employed for the separation of the substance. By this method about 18 gm. of the compound have been separated from somewhat more than two tons of fresh thyroid material which has been made up almost entirely of hog thyroid.

The yield of 18 gm. from more than two tons of material is obviously a

very small percentage of the theoretic. Now with all our knowledge of the chemical properties of the compound and the impurities we are able to secure a yield of 25 to 50 per cent of the theoretic. Only about 50 per cent of the total iodin in the gland is in the acid-insoluble constituents of the hydrolysis, and of this not more than 25 to 50 per cent is in a form which can be separated as pure crystals.

Concerning the 50 per cent of the total iodin in the thyroid which is soluble in acids after hydrolysis, it appears probable that this iodin is present in compounds which represent various stages in the elaboration of the completed product from iodin taken in with the food. Only complete elaboration of thyroxin renders it insoluble in acid, and only complete elaboration endows it with its specific physiologic activity.

PHYSICAL AND CHEMICAL PROPERTIES OF THYROXIN

The physical and chemical properties of pure thyroxin in crystalline form are as follows: The melting-point of thyroxin is 240 C. when the temperature is increased 10° per minute. The compound is colorless, odorless, and tasteless. It is soluble in sodium, potassium, and strong ammonium hydroxid, but in the dry crystalline form it is not soluble in sodium, potassium, or ammonium carbonate. It is precipitated from its alkaline solution by all acids stronger than and including carbonic acid. It is insoluble in all ordinary organic solvents. Slight solubility has been found with diethyl succinate, but it is very insoluble in alcohol, ether, petroleum ether, benzol, acetone, chloroform, carbon tetrachlorid, carbon disulphid, and glacial acetic acid. It is exceedingly insoluble in water. It is slightly soluble in strong hydrochloric acid. Its solubility in dilute hydrochloric acid is one part in 200,000. When precipitated by mineral acid, it forms a flocculent, amorphous, voluminous precipitate. If the acid solution containing the precipitate is heated, this may produce no effect. However, if sufficient acid is present, a change takes place, the precipitate becomes finely granular, crystalline in nature, and settles very rapidly to the bottom of the container.

A very remarkable property of the compound is its behavior in sodium hydroxid. It is practically indestructible in sodium hydroxid provided the temperature is not raised to too high a point. It is soluble in dilute sodium hydroxid. As the percentage is increased it becomes less and less soluble, and at between 15 and 20 per cent of sodium hydroxid the compound separates as a disodium salt. Further addition of hydroxid merely completes this precipitation so that the compound can be heated

to 100 C. in as h:gh as 50 per cent sodium hydroxid without altera-
tion, and it may be recovered simply by acidifying the solution.

The compound is soluble in alcohol containing hydrochloric acid,
but it is insoluble in alcohol containing acetic acid. A very convenient
method for its crystallization is to dissolve it either in alcohol contain-
ing hydrochloric acid to which sodium acetate is added, or in alcohol
containing sodium hydroxid, and then add acetic acid to this. It may
also be precipitated by boiling its ammoniacal aqueous or alcohol solu-
tion.

The compound crystallizes in several forms, depending on the solu-
tion from which it is crystallized. When crystallized out of alcohol by
adding acetic acid to its sodium salt, the crystals are generally curved
and in rosette form. The length of the needles varies with the tempera-
ture. When precipitated from a hot solution, they are longer than when
precipitated in the cold. When precipitated by boiling the ammoniacal
aqueous solution, the crystals are long, slightly curved blades, generally
in sheaf form. When precipitated by carbon dioxid out of water solu-
tion, an amorphous precipitate results unless the solution is warmed.
If carbon dioxid is passed through a warmed alkaline solution, crystals
of needle form result.

When acetic acid is added to the sodium salt of thyroxin in alcohol,
it separates in crystalline form. When hydrochloric or sulphuric acid is
added to the sodium salt of thyroxin dissolved in alcohol, no crystalliza-
tion occurs. Thyroxin therefore forms an alcohol-soluble salt with
mineral acids but not with acetic acid. The question suggested itself
whether the salt would retain the acid radical after precipitation from
water solution and drying. In order to determine this the compound
was precipitated by a slight excess of sulphuric acid added to the aque-
ous alkaline solution of the compound. The acid solution was heated
until the character of the precipitate changed from its amorphous form
to its heavy crystalline condition. Analysis of these crystals showed
that they contained 60 per cent of iodin. Analysis of the crystals pre-
cipitated from alcohol by acetic acid showed that they contained 65 per
cent of iodin. This difference in the percentage of iodin was shown to
be due to the formation of a salt with sulphuric acid. When the com-
pound is crystallized out of water by boiling its ammoniacal salt, it
separates in the free-base form and contains 65 per cent of iodin. When
it is precipitated by hydrochloric acid, it crystallizes in two forms: one
apparently is the hydrochlorid which separates in flat plates, the other

is the typical free-base form. The sulphate appears to be very stable and is not hydrolyzed by boiling in water in the presence of sulphuric acid. The hydrochlorid, however, is more easily hydrolyzed by water.

RÉSUMÉ OF PROPERTIES OF THYROXIN DETERMINED PRIOR TO ITS ULTIMATE ANALYSIS

1. The compound can be crystallized in two forms, one the free-base, and the other the salt form.

2. The percentage of iodin in the free-base crystals is 65.

3. The percentage of iodin in the sulphate crystals is 60.

4. From the percentage of iodin in the sulphuric salt and in the free-base the molecular weight of the compound is calculated to be 585.

5. The compound in its purest form gives a qualitative test for nitrogen.

6. After the alkaline fusion it gives the pine-splinter reaction, suggesting the presence of the indol nucleus.

7. Its solubility in alkalies and its acidic nature suggests the presence of the carboxyl group.

8. Its power of forming salts suggests an amino or imino group.

The compound gave the following results for the determination of carbon, hydrogen and nitrogen, and iodin (Table 1). From these results the empirical formula was determined to be C_{11}, H_{10}, O_3, N, I_3. From a study of the derivatives of thyroxin we have shown it to be tri-hydro-tri-iodo-alpha-oxy-indol propionic acid.

TABLE 1.—ANALYSIS

FOUND		CALCULATED FOR
		C_{11} H_{10} O_3 N I_3
C	23.32	C 22.57
H	1.74	H 1.72
O	7.61	O 8.20
N	2.23	N 2.39
I	65.00	I 65.10
Molecular weight found, 585		Molecular weight calculated, 584.8
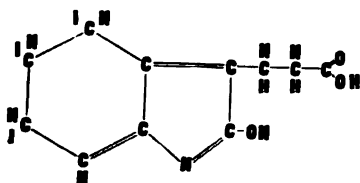
Fig. 116.—Structural formula for thyroxin in alkaline solution.
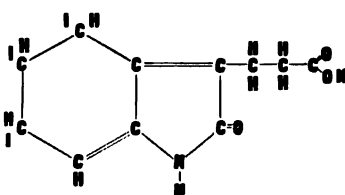
Fig. 117.—Structural formula for thyroxin in acid solution.

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Discussion of the Structural Formula

The Carboxyl Group.—Evidence for the carboxyl group in thyroxin is its acidic nature, its soluble alkaline salts and insoluble metal salts. The barium, copper, zinc, and silver salts of thyroxin have been made and studied microscopically. These compounds are all beautifully crystalline and insoluble in water. The barium salt is made by adding barium chlorid to a solution of the sodium salt of thyroxin. The others are formed by dissolving thyroxin in sodium hydroxid, adding ammonia, dissolving the copper, silver, or zinc salt in ammonium hydroxid, and adding the ammoniacal solution of the metal to the alkaline solution of thyroxin. At first an amorphous precipitate forms. This appears to redissolve in excess of the ammoniacal solution of the metal, and then to separate in beautiful microscopic crystals. Analysis of the silver salt for iodin and silver shows that not one but two atoms of silver have been added to the compound. One atom of silver without doubt was added to the carboxyl. The position of the second atom is discussed below.

The acidic property of thyroxin and the addition of two atoms of silver to the molecule are not conclusive proof of a carboxyl and hydroxyl group, as the same action could occur with two hydroxyl groups. The fact that there is a carboxyl is furnished by the dimethyl ester. Methyl iodid added to the di-silver salt of thyroxin forms the dimethyl ester. This is insoluble in sodium hydroxid. Heating with dilute alkali renders the compound soluble, but still one methyl group is attached and it will withstand severe alkaline treatment. The difference in the ease with which one methyl group saponifies is evidence that the two methyl groups are attached differently. Presumably one is attached to a carboxyl group, the other to a hydroxyl group.

The Imino Group.—The best evidence for the imino group is its formation of the ureid with cyanic acid. Thyroxin reacts with potassium cyanate in glacial acetic acid very readily, and forms a compound soluble in glacial acetic acid. Analysis of this compound agrees with that calculated for the ureid.

Evidence for the Existence of the Two Tautomeric Possibilities.— Tautomerism in the indol family is of common occurrence. In thyroxin there are two tautomeric possibilities—one the alpha-carbonyl group and the other the alpha-hydroxy group, with no hydrogen attached to the imino. When thyroxin is added to pyridene, to which semicar-

bazid hydrochlorid is added, semicarbazid does not react with the carbonyl group of thyroxin. Apparently the slight alkalinity of pyridene is sufficient to produce the enol form with which semicarbazid cannot react. When, however, the hydrogen on the imino group is substituted so that it cannot migrate and produce the enol form, the carbonyl group should form a semicarbazone. To show this, the hydrogen of the imino group was replaced with acetyl, the acetyl derivative was dissolved in pyridene, to which was added semicarbazid hydrochlorid, and under these conditions the compound very readily reacted to form a semicarbazone.

Evidence for the existence of the keto form with the hydrogen on the imino is furnished by the formation of the ureid with cyanic acid, and by the formation of the acetyl and formyl with acetic anhydrid and formic acid chlorid. A carbonic acid derivative may also be made by reacting with phosgene and with ethyl-formic-acid chlorid.

Another proof that the hydrogen exists attached to the imino group is furnished by the di-silver salt. Thyroxin forms a very characteristic silver salt with an ammoniacal silver solution, and analysis shows that two atoms of silver have been added. When, however, the hydrogen of the imino group is taken up by a derivative, it cannot be replaced, and theoretically the second silver atom cannot be added. It is interesting to find that no crystalline silver salt does form with the ureid, the acetyl, the formyl, or carbonic acid derivative made from phosgene. That thyroxin also forms a disodium salt is shown from the behavior of the derivatives in which the hydrogen of the imino has been replaced. The sodium salts of these derivatives are very sparingly soluble in sodium hydroxid. They are soluble in dilute sodium hydroxid, but if this is increased appreciably, the sodium salts separate in fine short crystals. This is true of the acetyl, the formyl, and the carbonic acid derivatives.

When it is possible for the enol form to exist, there is no doubt that the sodium adds to the hydroxy and not to the imino group.

Another reaction common to the derivatives attached to the imino group is their solubility in alcohol. Thyroxin is insoluble in ethyl alcohol, but the ureid, the acetyl, and all other derivatives produced by replacing the hydrogen of the imino are more soluble in alcohol.

The Evidence That the Carbonyl Group is on the Alpha Carbon to the Imino.—From a consideration of the structural formula of the compound, the carbonyl group could be on the side-chain in either the first or second carbon atom. If it were so placed, then reactions involving

the carbonyl group should not be affected materially by the imino group, since they would be separated by as many as three or four carbon atoms. It has been found, however, that the reactions with the carbonyl depend on the reactivity of the imino group. Until the hydrogen of the imino group has been replaced, no condensation with an amino group can take place.

The semicarbazone will not form when thyroxin is treated with semicarbazid in pyridene. The acetyl derivative of thyroxin readily reacts in pyridene with semicarbazid. It does not seem probable that the close relationship shown by these reactions could exist between the imino and the carbonyl groups if the carbonyl group were in any position other than on the alpha carbon.

Condensation Between the Carbonyl Group of Thyroxin and an Amino Group.—Beside the reaction between the carbonyl group and semicarbazid, it was of great interest and significance to effect the condensation between the amino group of glycin and the carbonyl group. This condensation will not take place when thyroxin and glycin are boiled together in pyridene, in glacial acetic acid, in ethyl or amyl alcohol. But if the acetyl derivative of thyroxin is dissolved in pyridene, it will react with great ease with the amino group of ethyl glycin hydrochlorid.

Of still greater interest is the reaction between the carbonyl group and the amino group of glycin when the carboxyl group of glycin is attached to the imino group of thyroxin. This is accomplished by treating thyroxin in glacial acetic acid with the acid chlorid of glycin hydrochlorid. The carboxyl group is thereby attached to the imino. When this is dissolved in pyridene, then the amino group of glycin readily reacts with the carbonyl group of thyroxin, the result being a ring compound of five members, between glycin, the imino group, and the alpha-carbonyl group.

The reaction between the amino group of glycin and the carbonyl group of thyroxin I regard as very significant in connection with the physiologic activity of thyroxin. It seems highly probable that this condensation is not specific for glycin, but will occur with any alpha-amino acid. This reaction, then, gives a definite chemical conception of the action of thyroxin, and as clinical and experimental results confirm this, it has seemed best to name the substance, bearing in mind the importance of the respective groups present. The name "thyroxin" was decided on from the evident desirability of emphasizing the presence of

the reactive carbonyl group. The name "thyr-oxy-indol" combines in a satisfactory manner the source of the hormone, the presence of oxygen and the mother substance, indol. "Thyr-oxy-indol" appears too bulky a word to stand every-day usage, and therefore has been abbreviated to "thyroxin," which we here suggest as the name of the thyroid hormone. Any reference to the presence of iodin in the hormone is purposely omitted from the name of the substance, because the work we have done concerning the physiologic action removes the attention from the iodin. Its function in the molecule appears merely to place it in its unique position in regard to acidity and basicity. The indol nucleus has feeble alkaline properties. Iodin added to the benzol ring produces more acidic properties. The hydro groups still further modify the reaction of the substance, so that the net result of the influence of the alpha-carbonyl, the iodin, and the hydro groups places the compound in a unique position in regard to acid and basic properties. It is so delicately balanced that the change in hydrogen-ion concentration between carbonic acid and pyridene is sufficient to affect the compound, producing one tautomeric form or the other. Since the compound always exists in equilibrium with its surrounding medium, the labile hydrogen must migrate from the imino to the carbonyl, changing it to hydroxy or the reverse with very slight changes of hydrogen-ion concentration. The function of the iodin in thyroxin is to increase the reactivity and sensitiveness of the functioning groups present, namely, the carbonyl and imino. Any other function of the iodin is highly problematic.

The fact that the compound exerts its influence within the animal organism for days after a single injection proves that it is not destroyed in carrying out its physiologic action and suggests that it acts as a catalyst.

A Consideration of the Reactions Involved in the Isolation of Thyroxin

Thyroxin was first separated by following a method of treatment which was found to progressively increase its iodin content, and for the isolation of much of the material so far prepared this same method was followed without any light being thrown on the exact nature of the chemical reactions involved. The determination of its empirical and structural formulæ now permits us to go back and explain these reactions.

The chain of events which led to the explanation of the reactions involved in the separation of thyroxin from the other compounds con-

tained in the acid-insoluble products of the alkaline hydrolysis was as follows:

First, it was found that derivatives attached to the imino group render thyroxin soluble in alcohol. This was found true of the acetyl, the formyl, the ureid, the sulphate, and the hydrochlorid. In the second place it was found that derivatives attached to the imino group do not form crystalline di-silver salts.

When thyroxin is partially purified, so that it contains from 30 to 50 per cent of iodin, it is soluble in alcohol. It does not form a crystalline silver salt. Pure thyroxin forms an insoluble barium salt. Partially purified thyroxin forms a soluble barium salt. These reactions suggested that the difficulty in purification arose from the fact that some derivative was attached to the imino group. This rendered the compound soluble in alcohol and, at the same time, by interfering with the formation of the typical barium salt, it prevented its precipitation with barium. Since it had already been shown that the sodium salt of the acetyl, the formyl, and other derivatives on the imino were readily thrown out of solution by increasing the amount of sodium hydroxid present, attempts were made to determine the group attached to the imino in the partially purified thyroxin by precipitating its sodium salt with a high concentration of sodium hydroxid. Partially purified thyroxin, containing about 40 per cent of iodin, was therefore dissolved in sodium hydroxid, and a solution of 30 per cent sodium hydroxid was added to this. As had been hoped, the addition of the stronger alkali soon produced a cloudy precipitate which did not settle but remained suspended, due to the high specific gravity of the solution. This was centrifugalized, the supernatant liquid contained most of the yellow impurities, and the precipitate remained in a firm felt in the bottom of the tube. It was dissolved in distilled water, sodium hydroxid was again added, the precipitate again formed, but this time the precipitate separated in more distinct particles and the solution was less turbid. It was centrifugalized, the supernatant liquid was still yellow, but showed much less color than the first solution. The residue in the bottom of the tube was again dissolved in distilled water, sodium hydroxid was again added, and this time the precipitate assumed a still different form, coming down in distinct separate particles, practically white, and the solution was almost colorless. These were examined under the microscope. They were the typical disodium salt of pure thyroxin itself, and not of a derivative. They were centrifugalized from the alkali, dissolved in alcohol, and pre-

cipitated by the addition of acetic acid, when they were recovered as pure crystalline thyroxin.

The substitution of sodium chlorid for sodium hydroxid permitted the solutions to be filtered instead of centrifugalized, and it was then found that sodium chlorid precipitated the disodium salt of thyroxin from an alkaline solution even better than did sodium hydroxid. This purification of thyroxin merely by the salting out of its disodium salt from the impurities threw a great deal of light on the chemical properties of thyroxin, and the nature of the impurities present. It explained why such variable results have been secured in the past, and why it was impossible to duplicate the first separation.

Investigation of the impurities which were separated from thyroxin by salting out the crystals from the alkaline solution showed that they are soluble in ether, that they are acidic in nature, and contain indol derivatives which give the pine-splinter reaction after fusion in caustic alkali. If pure crystalline thyroxin is dissolved in sodium hydroxid and some of these indol derivatives are added to the solution, there appears to be an immediate reaction, even in the alkaline, between thyroxin and these impurities which completely alters the chemical properties of thyroxin. The presence of these impurities renders thyroxin soluble in alcohol, and instead of separating with sodium chlorid as the crystalline disodium salt, it is thrown out of solution as an oily tar. This action we explain by the great reactivity of the imino group and the carboxyl group contained in these indol derivatives. That it is a very loose combination is shown by the fact that this oily tar, if dissolved in alkali, and again precipitated, will assume a slightly more crystalline appearance, and if reprecipitated several times, will eventually reappear as pure thyroxin. Therefore thyroxin, through its imino group, has the ability to form salts with weak organic acids. Although the bond of linkage between thyroxin and this as yet unknown indol derivative is very weak, it is sufficiently strong completely to prevent the separation of thyroxin in pure form.

The fact that the imino group of thyroxin combined so readily with the carboxyl group of some indol derivative raises the question of the reactivity of the imino group with aliphatic organic acids. It was found to be as follows: An alkaline solution of thyroxin, when treated with carbonic, acetic, or formic acid precipitates in free-base form without the formation of a salt. Thyroxin boiled in glacial acetic acid does not go into solution, and the acetate will not form in this way. Thyroxin will

dissolve when boiled in formic acid. However, when the excess of formic acid is boiled off, thyroxin separates, not as the formate, but in free-base form. Also when water is added thyroxin separates without retaining formic acid in the salt form. With lactic acid the action is a little different. Thyroxin is soluble in lactic acid, with which it forms some compound not hydrolyzed by water.

The relative inactivity of the imino group of thyroxin with the carboxyl group of acetic acid and formic acid is very interesting when the activity of the acetyl, where the acetate radical replaces the hydrogen of the imino, is considered. The imino group is thereby made more reactive and the acetate of the acetyl is readily formed. This is soluble in glacial acetic acid. On adding water only a partial hydrolysis of the acetate occurs.

The action of carbon dioxid during the purification appears to partially separate thyroxin from the acidic indol impurities. Thyroxin is precipitated by carbon dioxid at a point slightly in advance of the impurities, so that by alternate alkaline treatment with barium hydroxid and carbon dioxid precipitation thyroxin may be gradually separated. Treatment with alkali alone may or may not open the bond between the imino and the impurities, but whether it does or not is of little consequence if the bond is immediately reëstablished on acidification. In partially purified thyroxin the hydrogen of the imino is not replaced by any group, but the mode of linkage is probably the same as in the hydrochlorid or sulphate, the acid simply adding to the imino group.

Mention has been made of an indol derivative which is easily attached to and with difficulty removed from the imino group of thyroxin. This compound may be purified to some extent so that most of the brown color is removed, but it is an oily, amorphous tar with which it is exceedingly difficult to carry out any reactions toward its identification. The imino group of thyroxin appears to react with many other constituents of the thyroid split products. Some of these are heavy, complex black substances which totally change the properties of thyroxin. Some of these compounds render thyroxin insoluble in alcohol and insoluble in barium; others make it soluble in alcohol and soluble in barium.

It seems probable that the compound attached to the imino group which makes the product soluble in barium must contain a free carboxyl group. Partially purified thyroxin not only is soluble in barium hydroxid, but it is readily soluble in sodium carbonate. It is soluble in sodium carbonate until the imino group exists in free form. It is then insoluble.

The formation of the soluble barium salt and the solubility in sodium carbonate suggest that the compound attached to the imino group contains a free carboxyl.

The derivatives of thyroxin which have a substitution of the hydrogen on the imino group have another peculiarity which may be related to certain reactions observed in the purification. In the presence of sunlight these compounds develop a pink color and free iodin is broken off, so that the reaction appears to involve oxidation. This production of a pink color occurs with remarkable ease with the carbonic acid derivative made from phosgene. The acetyl derivative also readily develops a pink color; this same pink color we have observed many times to appear on some of the partially purified preparations of thyroxin. This is another indication that a derivative of some form is attached to the imino group in partially purified thyroxin. The production of a pink color also appears to involve some change in the carbonyl group. All derivatives in which the hydrogen of the imino is replaced and which therefore have a carbonyl group which cannot change to a hydroxy are much more reactive and are easily altered by heating in either strong acid or alkali. Although thyroxin can be heated in acid or alkali without alteration, derivatives, replacing the hydrogen of the imino group, when so treated, turn pink, yellow, or blue and are easily decomposed. These reactions are probably due to some condensation with the carbonyl group.

In regard to the effect of a high temperature on the acidification of an alkaline solution of partially purified thyroxin: the impure thyroxin is so altered that when it is redissolved in alkali, iodin is broken off. It seems probable that this action is because thyroxin exists in the keto form with the carbonyl group open. The effect of heat on the compound in this condition results in oxidation, with consequent splitting off of iodin. The mechanism by which carbon dioxid breaks off iodin when passed into a warm alkaline solution of partially purified thyroxin is undoubtedly the same. In the cold alkaline solution no oxidation and therefore splitting off of iodin occurs, but carbonic acid passed into the warm solution alters the hydrogen ion concentration so that this oxidation may take place.

PHYSIOLOGIC ACTIVITY OF THYROXIN

The literature concerning the physiologic activity of the thyroid presents a most confusing mass of statistics and experimental results.

Thyroid activity has been tested in the past by measuring the increase in pulse rate, changes in blood-pressure as shown by kymographic tracings, changes in nervous irritability, the production of gastric responses, the length of time for fatigue to result in a muscle, the resistance of white mice to acetonitrile, the effect on growth, the change in the rate of metamorphosis of tadpoles, the relief of symptoms of myxedema and cretinism, the increase in nitrogen elimination, change in the total metabolic rate, and the increase in the basa' metabolic rate. Simply the enumeration of the methods used in physiologic testing is an eloquent criterion of our knowledge concerning the function of the thyroid. To determine which of these effects are due to thyroxin and which are due to other constituents of the thyroid, to relate the effects which are due to thyroxin to a common cause and to simplify this cause to a chemical reaction with definite end products, is the task at hand.

A discussion of the physiologic testing of thyroid activity will be deferred until later in this article. The pharmacologic action of thyroxin as it is known to-day is as follows:

Upon injection of thyroxin in amounts up to 3 mg. per kilo into a dog there is no immediate apparent effect. There is no change in blood-pressure[5, 10, 14]; there is no increase in pulse-rate; there is no increase in nervous irritability. Nitrogen output is not altered. If but a single injection is given, there may be no visible response for a number of hours, the length of time varying with the experimental animal. At the end of from twelve to thirty-six hours there will be an increase in pulse-rate and a slight increase in nervous irritability, with increase in nitrogen and carbon dioxid output. In order to secure the maximum response to thyroxin, several successive daily doses have to be administered and the maximum response in the animal is found to occur several days after the first injection. By increasing the amount of thyroxin given and by altering the condition of the animal by excessive meat feeding or starvation, variations in this typical response can be produced which will shorten the time of the first visible response and will alter its course. One striking difference produced by varying the dosage is furnished by two goats. One goat received 11 daily injections, of 9 mg. per day, at the end of which time it died. The other goat received 150 mg. at a single injection. The cardiographic tracing showed that there was a response which came on within a few hours, but this rapidly subsided, and within two or three days the goat showed no visible effects of the injection. Severe headaches, nausea, and diarrhea are produced

if large doses are given to individuals; a sense of increased ability and well-being is produced if small doses are given. Growth may be stunted with tremendous overdosing with thyroxin. Cretins may be made to grow as much as four inches in six months under proper dosage.

The injection of thyroxin is followed by three fundamental changes: One is the increased output of carbon dioxid, out of proportion to the nitrogen excretion; the second is increased elimination of nitrogen; and the third is the increased nervous irritability and greatly increased pulse-rate. The relation between these three phases of thyroid response has not yet been established and will not be discussed in this article.

Administration of thyroxin results in a revolution to the myxedematous patient and the cretin.[12] Every cell in the body responds. The effect is not localized in any organ or system of organs. Possibly our most rigid test for thyroid activity is furnished by the cretin and by myxedema. Administration of desiccated thyroid in this condition results in a practical cure in 100 per cent of cases. In testing any thyroid split product it must produce as great an effect, or the only conclusion remaining is that there is more than one active constituent in the thyroid. The effects of feeding desiccated thyroid to cretins and myxedematous patients are recorded in the literature for the past twenty-five years. The results are made certain from the very large number and the striking nature of the relief of symptoms.

Accepting this as at least one necessary criterion, preparations of split products of the alkaline alcoholic hydrolysis (described hereinbefore) were given to cases of cretinism and patients suffering from myxedema. It was found that the acid-insoluble constituents, even in their most impure form, were able to relieve the conditions with the same striking effects and in as complete a manner as desiccated thyroid itself.[12] This finding was the most encouraging stimulus for the persistent and continued investigation of the acid-insoluble constituents. The alcoholic alkaline hydrolysis was as severe in its chemical action as any step which would probably have to be applied for the separation of the iodin compound from the acid-insoluble constituents. The physiologic activity, therefore, having withstood the initial hydrolysis, it was reasonable to expect that it would withstand other treatment which would be necessary for its separation.

Experimentally, thyroxin in all stages of purity from the products of the first hydrolysis up to and including the pure crystalline form, con-

taining 65 per cent of iodin, was shown to possess the same physiologic activity when tested with the cretin and myxedematous patient.

Another method which has been used to test the physiologic activity of the thyroid hormone is the effect on the nitrogen excretion and the pulse-rate of dogs. Here, again, administration of thyroxin in all stages of purity from the first step of the hydrolysis up to and including the pure crystalline form produces an increase in nitrogen elimination, very marked increase in pulse-rate, and increase in nervous irritability, frequently with production of a tremor in the animal. Finally, thyroxin has been tested and has been shown to increase the basal metabolic rate, not only of myxedematous patients, but of normal persons.

Probably the most significant, and indeed fascinating, effect of thyroxin is its tremendous influence upon basal metabolic rate. Administration of thyroxin will increase basal metabolic rate from 40 per cent below normal[20] to a figure which is limited only by compatibility with life. This is so striking that on this property alone the proof that thyroxin is the active constituent of the thyroid could be rested.

These results, then, show that the physiologic activity of desiccated thyroid can be produced by the administration of a single pure crystalline compound of known composition. Furthermore, there is no physiologic effect of desiccated thyroid which cannot be produced by this same substance. That the action is specific for thyroxin has also been tested by administration of all the constituents of the thyroid other than thyroxin to cretins and myxedematous patients. It is interesting to find that there is no relief of any symptom specific to the myxedematous patient* by the administration of all the split products[10] other than thyroxin.

A Discussion of the Chemical Reactions Concerned with the Function of the Thyroid

In the previous pages of this article the isolation of thyroxin has been detailed and its physiologic effects have been shown. On these results one may form a tentative hypothesis of the function of the thyroid. While thyroxin has not been synthesized in sufficient amount to establish its structural formula beyond doubt, still work toward this end has

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* The symptoms in myxedematous patients relieved by the B fraction of the thyroid split products has been shown to be not specific to the condition of myxedema. This phase of the physiologic activity of the thyroid will not be discussed at this time, although evidence has been accumulated showing that there is an effect in some skin conditions by the products of the thyroid other than thyroxin.

progressed to a point which has practically confirmed its structural formula, and no single derivative or chemical reaction has been found which has not confirmed the formula assigned. I therefore base this proposed function of the thyroid mainly on the knowledge gained of its structural formula. It has already been shown that the two reactive groups in thyroxin are the carbonyl and the imino. These two groups therefore must be capable of explaining the chemical reactions involved by the functioning of thyroxin. These reactions must explain the function of the thyroid, and this in turn must explain the revolutionary changes which are the end results from administration of thyroxin to cases of cretinism and myxedema.

Experiments in vitro have shown that the carbonyl group of thyroxin is capable of reacting with the amino group of an alpha-amino acid. If it is the function of thyroxin to react with an amino group and the carboxyl group, there are three possible results of this reaction: (1) is deaminization, (2) is decarboxylation,[11] and (3) is both. The alpha-amino group having condensed with the carbonyl of thyroxin, and the carboxyl having been taken up by the imino group, a ring of six members will be formed. By a shift in the stresses of this ring it could be broken with elimination of ammonia, by the elimination of carbon dioxid, or by the elimination of both. Which one would occur would depend on the surrounding medium. The details of this action cannot be discussed as yet, but that the carbonyl group and the imino group are involved in the function of thyroxin it is possible to prove.

The introduction of pure thyroxin into an animal organism results in a definite response which can be measured by the increase in carbon dioxid output, the increase in the nitrogen output, and, under some conditions, by the greatly increased pulse-rate and increased nervous irritability. If the introduction into an animal organism of a derivative of thyroxin in which the hydrogen of the imino was replaced by other groups produced no physiologic response, this would be evidence that the imino group is essential for the functioning of thyroxin. Derivatives of this type have been injected, and while the work must be still further investigated, the results were sufficiently striking to report at this time. The introduction of thyroxin produced a very marked effect on the pulse-rate and nervous irritability of a dog. The injection of the ureid and the acetyl, in both of which the hydrogen of the imino was replaced by another group, produced no visible effect on the animal. The pulse-rate did not increase, there was no development of tremor or nervous irrita-

bility of any kind   Injection of thyroxin raised the pulse-rate from 100 to 220 per minute; injection of the acetyl and ureid did not increase the pulse-rate as much as 10 points.

If iodin per se is the essential portion of the thyroid hormone, merely replacing the hydrogen of the imino group by a derivative would probably not alter the effect of the iodin in the hormone, and it should function just as well whether or not the hydrogen of the imino were replaced. We find, however, that substitution of the hydrogen of the imino renders the substance inert. Iodin, of all the halogens, appears to make the balance of the two tautomeric possibilities existing in the thyroxin grouping the most delicate. Other groups introduced in place of the iodin would, in all probability, not greatly affect the gross chemical possibilities, but they would certainly alter the delicacy of its responding to a change in the hydrogen-ion concentration of the medium in which it is present.

It has been pointed out that the imino group of thyroxin is easily affected by certain impurities which occur in the products of hydrolysis of the thyroid. It has also been shown that mineral acids in a hot solution produce some reaction which renders thyroxin sensitive to subsequent alkaline treatment. It seems very probable that this is because, in the presence of the acid, the hydrogen of the imino has been replaced by some derivative. Since it has been shown that thyroxin derivatives which have the hydrogen of the imino replaced lose their physiologic activity at least in part, this action of acid forming a derivative with the imino group could very satisfactorily explain the loss of physiologic activity of iodothyrin.

In regard to the relation between thyroxin and decarboxylation, carbon dioxid output has been quantitatively associated with the amount of thyroxin within the animal organism.[20] In eight cases of myxedema Plummer has shown that the increase in the basal metabolic rate holds a mathematical relation to the amount of thyroxin administered, and this relation did not differ by as much as 3 per cent in the eight cases. Increase in basal metabolic rate and decarboxylation are not synonymous when applied to any single substance, but the great reactivity of the imino group of thyroxin with the carboxyl group and the direct mathematical and quantitative relation between carbon dioxid output and thyroxin permit of considerations of thyroid activity in terms of chemical reactions hitherto impossible. In a discussion of the physiologic activity of any thyroid split product this tremendous influence on basal metabolism must

iONS IN THE CERVICAL SYM-
iLIA IN RELATION TO
iALMIC GOITER*

B. WILSON

the clinical manifestations of which are
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that removal of the gland arrests the symp-
not absolute proof that the thyroid is the
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erfunction of the thyroid the result of primary
the gland itself or of direct stimulation from
on's experimental production in cats of some
ophthalmic goiter by continuous stimulation of
sympathetic system suggests the latter. Du-
that in all cases of exophthalmic goiter we have
examine there is a pronounced and constant
cervical sympathetic ganglia from which the
tire nerve supply. There is much suggestive
pathologic changes in the cervical sympathetic
direct bacterial infection within the ganglia.
present series of experiments has been to determine
the cervical sympathetic ganglia and indirectly
arious forms of stimulation applied to the ganglia
animals. Goats have been used for the experi-
ly, and the results on these animals only will be

5. Fawcett, G. G., Rogers, J., Rahe, J. M., and Beebe, S. P.: The effect of thyroid extracts upon blood pressure. Am. Jour. Physiol., 1914–1915, xxxvi, 113–125.
6. Gudernatsch, T. F.: Studies on internal secretion. IV, Treatment of tadpoles with thyroid and thymus extracts. Anat. Rec., 1916–1917, 357. (Proc. Am. Assn. Anatomists.)
7. Hunt, R.: The influence of thyroid feeding upon poisoning by acetonitrile. Jour. Biol. Chem., 1905, i, 33–44.
8. Hunt, R., and Seidell, A.: Studies on thyroid. I. The relation of iodin to the physiological activity of thyroid preparations. United States Hygienic Laboratories, Bull. No. 47, 1908.
9. Kendall, E. C.: A method for the decomposition of the proteins of the thyroid, with a description of certain constituents. Jour. Biol. Chem., 1915, xx, 501–509.
10. Kendall, E. C.: A method for the decomposition of the proteins of the thyroid, with a description of certain constituents. Tr. Am. Assn. Phys., 1915, xxx, 420–449.
11. Kendall, E. C.: The function of the thyroid parathyroid apparatus. Jour. Am. Med. Assn., 1916, lxvi, 811–813.
12. Kendall, E. C.: Studies of the active constituent, in crystalline form, of the thyroid. Tr. Assn. Am. Phys., 1916, xxxi, 134–145.
13. Koch, F. C.: On the nature of the iodin-containing complex in thyreoglobulin. Jour. Biol. Chem., 1913, xiv, 101–116.
14. Levy, R. L.: Studies on the conditions of activity in endocrine glands. IV. The effect of thyroid secretion on the pressor action of adrenin. Am. Jour. Phys., 1916, xli, 492–512.
15. Marine, D., and Feiss, H. O.: The absorption of potassium iodide by perfused thyroid glands and some of the factors modifying it. Jour. Pharmacol. and Exper. Therap., 1915, vii, 557–576.
16. Oswald: Zur Kenntniss des Thyreoglobulin. Ztschr. f. physiol. Chem., 1901, xxxii, 121–141.
17. Picke, E. P., and Pineles, F.: Untersuchungen über die physiologisch wirksame Substanz der Schildrüse. Ztschr. f. exper. Path. u. Therap., 1909–1910, vii, 518–531.
18. Plummer, H. S.: Blood pressure and thyrotoxicosis. Tr. Assn. Am. Phys., 1915, xxx, 450–457.
19. Plummer, H. S.: The function of the thyroid, normal and abnormal. Tr. Assn. Am. Phys., 1916, xxxi, 128–133.
20. Plummer, H. S.; The physiologic function of the thyroid. Paper presented before the Federation of American Societies for Experimental Biology, December 29, 1917.
21. Rogers, J.: Discussion on experimental hyperthyroidism. Jour. Am. Med. Assn., 1917, lxix, 618.
22. Rogers, J., Rahe, J. M., Fawcett, G. G., and Hackett, G. S.: The effects upon the gastric secretion of organ extracts. Am. Jour. Physiol., 1915, xxxix, 345–353.
23. Fawcett, G. G., Rogers, J., and Beebe, S. P.: The active principles of different organs as shown in kymograph tracings. Am. Jour. Physiol., 1915, xxxvii, 453–461.
24. Vaughan, V. C.: Protein split products in relation to immunity and disease. Philadelphia, Lea, 1913, 476 pp.

EXPERIMENTAL LESIONS IN THE CERVICAL SYM-
PATHETIC GANGLIA IN RELATION TO
EXOPHTHALMIC GOITER*

L. B. WILSON

That exophthalmic goiter, the clinical manifestations of which are due essentially to a greatly increased protein metabolism, is the joint result of disturbance in the several glands concerned with metabolism, there can be little doubt. The fact that the thyroid shows a pronounced and constant series of functional changes parallel with the course of the disease, and the further fact that removal of the gland arrests the symptoms, is convincing though not absolute proof that the thyroid is the secretory gland the hyperfunction of which initiates the metabolic disturbance.

But is the primary hyperfunction of the thyroid the result of primary pathologic change within the gland itself or of direct stimulation from its nerve supply? Cannon's[1] experimental production in cats of some of the symptoms of exophthalmic goiter by continuous stimulation of the thyroid through the sympathetic system suggests the latter. Durante and I[2] have shown that in all cases of exophthalmic goiter we have had an opportunity to examine there is a pronounced and constant pathologic lesion in the cervical sympathetic ganglia from which the thyroid receives its entire nerve supply. There is much suggestive evidence that these pathologic changes in the cervical sympathetic ganglia are the result of direct bacterial infection within the ganglia.

The object of the present series of experiments has been to determine the effect directly upon the cervical sympathetic ganglia and indirectly upon the thyroid of various forms of stimulation applied to the ganglia themselves in healthy animals. Goats have been used for the experiments almost exclusively, and the results on these animals only will be

described herein. The goat is a very desirable animal for experiments on the sympathetic ganglia and the thyroid, since the tissue-elements of both these organs in their normal and pathologic morphology and their staining reactions closely resemble those of the tissue-elements of the same organs in man.

Stimulation in some of the experiments has been produced by electricity; in most instances, however, the stimulus has been obtained by direct bacterial inoculation into the ganglia. Observations have been completed on 19 goats, and are still in progress on 6 others.

Technic

Electric stimulation.—After proper etherization of a goat, its right superior cervical sympathetic ganglia were exposed. The ganglion was then directly stimulated by a moderate tetanizing current for one second at intervals of three seconds for a period of one hour. During the experiment the animal's blood-pressure was taken and the amount of saliva excreted noted. After one hour the right cervical ganglion and the right lobe of the thyroid were removed with as little loss of blood as possible. The left superior cervical sympathetic ganglion was then exposed and stimulated in the same manner as the right had been, but for a period of five and one-half hours. At the end of five and one-half hours the left superior cervical sympathetic ganglion and the left lobe of the thyroid were removed. After removal the ganglia and the lobes of the thyroids were properly fixed and stained by various methods, the ganglia usually by Nissl's and Ramon y Cajal's methods, and the thyroid with hematoxylin-eosin and by Bensley's acid-fuchsin-methylene-green after acetic-osmic-bichromate fixation.

Bacterial stimulation.—After properly etherizing a goat, its right or left superior cervical sympathetic ganglion was exposed and a small quantity of a culture of some bacterium was injected into the capsule of the ganglion. The wound was closed with aseptic precautions, and the goat placed under observation. The period of observation varied from three days to three months. A few of the animals died, and in such instances complete postmortems were made. In some of the others the cervical sympathetic ganglia and the lobes of the thyroid from both sides were removed at operations. In the remainder of the goats only the injected ganglion and the thyroid lobe on the same side were removed and examined.

Summary of Observations

1. The normal nerve-cells of the cervical sympathetic ganglia in the adult goat closely resemble the normal nerve-cells of the cervical sympathetic ganglia of the human adult, except that a relatively large number of them are binucleate. Similarly, the thyroid of the adult goat when at rest histologically closely resembles the resting adult human thyroid.

2. (a) Moderate electric stimulation applied for one second at intervals of three seconds for a period of one hour to the superior cervical sympathetic ganglion of an adult goat appears to produce no marked changes in the blood-pressure or respiration. If there were any definite changes, they were masked by the diffuse stimulation involving the vagus. There was marked salivation. (b) Microscopically, after the electric stimulation noted above, a large number of the nerve-cells of the stimulated ganglion were swollen and showed hyperchromatization. The demonstration of dissolution of the chromatin by Nissl's method, or of the presence of lipoid changes by Sudan III and Ramon y Cajal's methods, has not been possible in any of the cells. (c) After the above-mentioned stimulation the cells of the thyroid parenchyma were found swollen, their protoplasm distinctly granular, and their nuclei well rounded. The acini were distended with a feebly staining secretion, the numerous large vacuoles in stained preparations of which indicated the liquid character of the secretion. The condition of the cells and colloid secretion was parallel in all respects to that found in the thyroids of early cases of exophthalmic goiter in the human subject.

3. (a) Moderate electric stimulation applied to the superior cervical sympathetic ganglion for one second at intervals of three seconds throughout a period of five and one-half hours produced clinical changes similar to those noted in paragraph 2. (b) Microscopically, after the electric stimulation noted above, many of the nerve-cells were markedly swollen and showed intense hyperchromatization. Many were swollen, hydropic, and with disseminated chromatin. Sudan III preparations, even when thoroughly differentiated, showed conclusive evidence of lipoid change. This was demonstrated by Ramon y Cajal's method. (c) After the above-mentioned stimulation, the cells of the thyroid parenchyma were found swollen, but not nearly so much so as in those thyroids in which stimulation had been applied for only one hour. The protoplasm was clear, and the nuclei showed a tendency to crenation.

The acini were usually more distended, and were filled with colloid material which was more densely stained and contained fewer vacuoles than that noted in paragraph 2 (*b*). These changes were evidently the result of beginning exhaustion of the cells, and resembled the changes in the thyroid in cases of exophthalmic goiter in the human subject in which remission of symptoms has already begun.

4. (*a*) After the injection of a virulent culture of Streptococcus hemolyticus into the capsule of the superior cervical sympathetic ganglion of goats, the animals died within three days after exhibiting symptoms of an intense toxemia. (*b*) Within the injected ganglion of such a goat the nerve-cells were found to lie in greatly distended pericellular lymph-spaces. They were markedly hyperchromatic and hydropic, with diffuse dissemination of the chromatin, or were more or less completely disintegrated. No evidence of lipoid change was demonstrated by the Sudan III or silver-impregnation methods. (*c*) After the above injection, the cells of the thyroid parenchyma were palely staining, not swollen, and apparently not overfunctioning. The amount and character of the colloid within the acini was not distinguishable from normal.

5. After the injection of certain strains of Bacillus influenzæ of apparently low virulence, no systemic reaction or histologic lesions were demonstrated. After the injection of other strains more recently isolated a marked inflammatory reaction was found around the injected ganglia, though the goats had shown no symptoms. Changes within the ganglia and within the thyroid were indistinguishable from those within the ganglia and thyroids from the goats described in paragraph 6.

6. (*a*) The injection of freshly isolated virulent cultures of Bacillus bronchisepticus into the superior cervical sympathetic ganglion of adult goats usually produced marked constitutional symptoms, such as trembling, increase of temperature, and loss of appetite, and frequently caused death in from three days to three weeks. No exophthalmos was noted. (*b*) Within the injected ganglion of such a goat many of the nerve-cells in animals dying early were found to be markedly hyperchromatic; others were hydropic, with disseminated or invisible chromatin and more or less distorted nuclei within such cells. Sudan III and silver-impregnation preparations showed the presence of changed lipoids. In the ganglia of goats that lived three weeks or more there was unmistakable evidence of complete cell-destruction, in some instances extending from the point of inoculation well into the ganglion.

Lipoid pigmentation was distinctly shown by Sudan III and silver impregnation. Histologically, these changes were parallel to those found in the ganglia in cases of exophthalmic goiter in the human subject. (c) In goats from which the thyroid had been removed in from three days to three weeks after the injection the cells of the thyroid parenchyma were actively functionating, as was evidenced by their swollen size, granular protoplasm, well-rounded nuclei, and the presence of large quantities of feebly staining secretion within the acini. The histologic appearance was closely parallel with that found in the thyroid in early cases of exophthalmic goiter. When a period of three months had elapsed between inoculation and removal of the thyroid, the thyroid parenchyma showed evidence of exhausted function in that the cells were no longer swollen, their nuclei were more or less crenated, and the colloid secretion within the acini was densely staining.

Conclusion

From the above experiments it would appear that irritation from the presence of certain bacteria within the cervical sympathetic ganglia of the goat may produce histologic pictures within the ganglia and in the thyroid which parallel those found in the various stages of progressive and regressive exophthalmic goiter. This evidence supports the suggestion that in exophthalmic goiter the thyroid receives its stimulus to overfunction through its nerve supply, and as a result usually of a local infection in the cervical sympathetic ganglia.

REFERENCES

1. Cannon, W. B., Binger, C. A. L., and Fitz, R.: Experimental hyperthyroidism. Amer. Jour. Physiol., 1914–15, xxxvi, 363–364.
2. Wilson, L. B., and Durante, L.: Changes in the superior cervical sympathetic ganglia removed for the relief of exophthalmos. Jour. Med. Res., 1916, n. s., xxxiv, 273–296.
   Wilson, L. B.: The pathologic changes in the sympathetic system in goiter. Am. Jour. Med. Sc., 1916, clii, 799–812.
   Wilson, L. B.: Further study of the histopathology of the autonomic nervous system in goiter. Jour. Lab. and Clin. Med., 1917, ii, 295–307.

DIABETES AND THE PRACTITIONER*

D. M. BERKMAN

In an attempt to determine the amount of treatment, and in some measure place the responsibility for the faulty treatment of diabetes in general practice, the histories of 100 consecutive cases of proved glycosuria were analyzed. There were 54 males and 46 females. Grouped in decades in respect to age they were as follows:

Decade	1	2	3	4	5	6	7 and above
Number of patients	1	4	6	11	21	32	24

Thus it is seen that the occurrence of diabetes steadily increases with each decade up to the sixth, when it reaches its maximum. This may be explained in two ways: First, undoubtedly diabetes is initiated most frequently in the fifth and sixth decades. Second, it is during this period that, with beginning deterioration of general health, the greatest number of persons report for general examination. It is astonishing that the occurrence does not drop more decidedly following the sixth decade, as the rate of life persistence drops appreciably and increasingly. Furthermore, fewer persons in this period think it worth while to report for examination. Twenty-two patients in the series were suffering from the more or less acute or rapidly progressive type of the disease. Their average age was thirty-seven years; the oldest was sixty-eight. The other seventy-eight had the more chronic type characteristic of diabetes in middle and later age.

Forty-one patients had no previous knowledge of glycosuria. Of these, 31 gave more or less indefinite histories, while 10 gave histories unmistakably characteristic of diabetes. It could not be estimated with any approach to accuracy how many of these 41 patients had had previous examination by one or more physicians. However small this number may be, it is too large.

Fifty-nine patients had previous knowledge of diabetes varying from

a few weeks to ten years.   In 17 instances there had been no effort at dietary treatment, although several patients had been given "medicine to cure diabetes."   Of the 42 cases in which treatment had been instituted, 21 patients had made more or less successful efforts to stick to the diet and follow directions.   The other 21 had either dropped treatment entirely or lapsed into an inadequate desultory type of dieting, evidently futile.   Clearly the faults in treatment may be summed up as follows:

1. Lack of universal routine urinalysis.   Glycosuria can be discovered by one of the simplest and most easily performed laboratory tests ever devised, namely, the Haines test.   Urinalysis is well taught in every reputable medical school in the United States.

2. Lack of coöperation of physician with the patient after the diagnosis has been established.   Physicians are apparently reluctant to devote sufficient time and thought to the purpose of establishing a diet at least approximately suitable.   So often the patient with diabetes is told that he must avoid sugars and sweets, and that nothing further can be done.   The patient, considering himself incurable, becomes completely discouraged, and sits down to await the end with as much comfort as possible.

3. Lack of coöperation of the patient with the physician.   With very few exceptions this is directly due to the reasons indicated in the preceding paragraph, or to failure on the part of the physician to impress his patient with the fact that although from one standpoint diabetes is an incurable disease, in a large majority of cases it is so controllable that life may be indefinitely prolonged in comparative comfort, and distressing crippling sequelæ, such as gangrene, optic neuritis, and cataract, may be frequently avoided.

I would mention here that juvenile diabetes, while a grave condition, is not always necessarily fatal.   Riesman reports cases of a type with low glycosuria, high tolerance, and mild symptomatology, which responded to diet very gratifyingly.

In the decades in which diabetes is most frequent, the greatest and most lasting results may be obtained by the maintenance of a proper diet.   This is a most pertinent and significant fact.   During recent years, advance in the therapeusis of diabetes has been given great stimulus by two brilliant investigators—Allen in the experimental field and Joslin in the clinical.

Joslin's work has been especially acceptable to the practitioner

because it has provided him with diet tables, food values, and a working knowledge of their application. Allen's valuable contribution has been in working out the safety, practicability and great value of starvation treatment, which was conceived, attempted, and discarded many years previously.

After the diagnosis has been settled it is necessary to secure the absolute coöperation of the patient by carefully educating him in the theory and essentials of his treatment. The severity and gravity of the case should then be carefully estimated, so that abrupt changes in diet may not precipitate serious consequences. With attention to these details, the urine is rendered sugar free as rapidly as possible. In accomplishing this, forty-eight hours of starvation are exceedingly efficient. During starvation, water *ad libitum* is allowed, also bouillon or clear meat broths, the use of salt being encouraged, and small amounts of whisky if desired. In doubtful cases Joslin advocates a prestarvation period of from several days to a week or two, during which time fats and oils are first subtracted from the diet, and afterward the carbohydrates are diminished. Starvation is then begun. Following the starvation the urine will usually be found sugar free. There should then be instituted a mixed protein and green vegetable diet, low in fats and small in amount. Tolerance may be established by gradually adding known amounts of a uniform carbohydrate-containing food until sugar appears in the urine.

From here on the purpose becomes twofold: First, to raise tolerance as much as possible by keeping well below the tolerance threshold. Second, to maintain nourishment, providing as acceptable and variant a diet as possible. This is readily done with standardized food tables, many of which have been published. During the period of observation, needless to say, frequent urinalysis is imperative. After the period of observation has been completed and tolerance established, it becomes necessary to create a diet suitable for that particular patient, on which he must exist until future developments give cause for a change. It has been my own experience that a steady diet, day after day, is not only monotonous, but also apt to lose its initial safe relation to tolerance.

In its place we have used a routine week's cycle, initiating it with one day of starvation followed by one or two days of rather strict diet, and ending it with at least one day of fairly liberal diet. This scheme is open to many variations, and is especially applicable to the use of an

oatmeal day. It also has the advantage of being more acceptable to the patient for long periods.

If the patient has been thoroughly impressed with the importance of his treatment, he will, on his own initiative, report at intervals for urinalysis and any necessary alterations of diet.

The question as to whether or not the patient should be taught to test his own urine must be settled according to the merits of the individual case. There are advantages and distinct drawbacks. Patients with strong nervous tendencies should not be allowed to test their own urine. The reason for this is self-apparent. Fright, shock, and nervous excitement undoubtedly play a rôle in the causation of diabetes.

In Joslin's most recent work he has compiled an interesting series of statistical records which, taken as *prima facie* evidence, seemingly show that diabetes is on the increase. However, their probable meaning is that urinalysis is becoming more common and that greater numbers of persons are coming for examination. This fact at least is clear: Diabetes is prevalent in all parts of the cilivized world. Its presence can be neither evaded nor ignored. Only in small part can it be treated by the sanitarium or the specialist. Let us face the fact, therefore, that the responsibility for the diagnosis and treatment of diabetes rests with the practising physician, who would do well to equip himself to the best of his ability, to cope with this really most amenable condition.

TABLE

Males, 54; females, 46.

Decades	1	2	3	4	5	6	7 and above
Number	1	4	6	11	21	32	24

Acute type, 22 patients; average age, 37 years

No previous knowledge of glycosuria, 41 { 31 no diabetic symptoms
{ 10 definite diabetic symptoms

Previous knowledge of glycosuria, 59 { 17 no treatment
{ 42 treatment { 21 maintained
{ 21 not maintained

Depreciation of general health due to diabetes, 48
General involvement of nervous system, 9
Definite changes in eyes, 6
Gangrene, 1

THE ACTION OF ADRENALIN IN INHIBITING THE FLOW OF PANCREATIC SECRETION*

F. C. MANN AND L. C. McLACHLIN

Benedicenti was the first to observe that adrenalin inhibited the flow of pancreatic juice. He noted that the subcutaneous injection of adrenalin decreased the flow of pancreatic secretion from pancreatic fistulas in dogs for a considerable length of time. Independently, Pemberton and Sweet observed the same action of adrenalin. They studied the effect of injection of adrenalin and extracts of various organs on the flow of secretion from a pancreas stimulated by intermittent injections of secretin. From the results of their experiments they conclude that the inhibition of pancreatic secretion by adrenalin is independent of the rise in general blood-pressure, that it is probably specific, and that one of the functions of the adrenals may be an antagonistic action toward the pancreas.

Edmunds repeated the work of Pemberton and Sweet, and studied the action of many other drugs on the rate of pancreatic secretion from a pancreas stimulated by a continuous injection of secretin. He found that practically all drugs or mechanical procedures which increased general blood-pressure decreased the flow of pancreatic juice. However, some drugs, such as adrenalin, produced a greater and more prolonged inhibition of pancreatic secretion than others. Plethysmographic tracings of the pancreas showed that the drugs having the more effective action produced a greater and more prolonged constriction of the pancreatic vessels. Edmunds concluded that adrenalin inhibited pancreatic function by producing anemia of the organ.

In a research on the general problem of the possible interrelation of the adrenals to the pancreas one of us (Mann) became interested in the action of adrenalin on pancreatic secretion. The results of several experiments dealing with this problem were practically the same as those obtained by Edmunds. However, the work of Edmunds was done

before the depressor action of adrenalin had been demonstrated and, in fact, only the large pressor doses of the drug were used in all previous investigations of this subject.   It seemed desirable to study the effect of very small doses of adrenalin, particularly doses which would produce a depressor action on the blood-pressure and on the flow of pancreatic juice.

The animals used in the research were dogs and cats.   They were fasted from eighteen to twenty-four hours before experiments were begun.   All the experiments were performed under urethane or ether anesthesia, the latter being administered by means of the Connell apparatus.   The ether tension varied between 36 and 44.   Carotid blood-

Fig. 118.—Kymograph record of blood-pressure and rate of pancreatic flow.
Time in minutes and seconds. The injection of 1 : 500,000 adrenalin solution decreased blood-pressure from 105 tc 75 and decreased pancreatic flow from 0.26 c.c. the minute before injection to 0.23 c.c. the minute during injection, and 0.20 c.c. the minute following injection.

pressure was recorded by a mercury manometer.   Both vagi were always sectioned.   The pancreas was stimulated by secretin prepared by the original method of Bayliss and Starling.   In order to obtain a uniform flow of pancreatic juice it was found best to use the continuous injection of secretin as employed by Edmunds.   In practice, however, Woodyatt's continuous injection apparatus was found to be of great value.   The secretin was injected quite rapidly until the gland began to secrete; it was then decreased to a rate which just maintained a moderate flow of pancreatic juice.   In this manner it was often possible to have an active gland with a normal general blood-pressure.   The flow of pancreatic juice was measured by placing in the major pancreatic duct a cannula connected with a glass tube graduated in 0.01 c.c.   One

observer devoted his full time to recording the flow of secretion by means
of a signal magnet. When cats were used, the adrenalin was adminis-
tered in exactly the same manner as that employed by Cannon and
Lyman in regard to the strength of the solution, the dose, and the rate
of injection. The technic of injecting with a buret, as Hoskins describes,
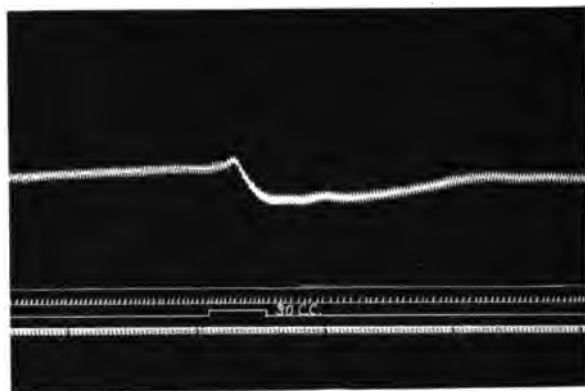
Fig. 119.—Kymograph record of blood-pressure and rate of pancreatic flow.
Time in minutes and seconds. The injection of 30 c.c. of 1 : 500,000 adrenalin solution decreased blood-
pressure from 105 to 75, and decreased rate of pancreatic flow from 0.27 c.c. the minute preceding the injection
to 0.27 c.c. the minute during the injection, and 0.20 c.c. the minute following injection.
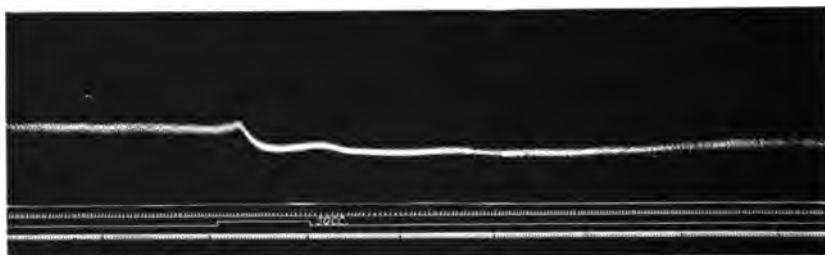
Fig. 120.—Kymograph record of blood-pressure and rate of pancreatic flow.
Time in minutes and seconds. The injection of 50 c.c. of 1 : 500,000 adrenalin solution decreased blood-
pressure from 90 to 70, and decreased rate of pancreatic flow from 0.31 c.c. the minute preceding the injection to
0.26 c.c. the minute during the injection, and 0.18 c.c. the minute following injection. Blood-pressure and rate
of secretion were both very slow to recover.

was used in the experiments on dogs. The strength usually employed
was 1:500,000, and only fresh solutions were used.

We were not uniformly successful in obtaining the depressor action
of adrenalin. This may have been due to several causes, chief of which
was the fact that the usual preparation of secretin decreases blood-
pressure. We were never able to obtain the depressor action of adrenalin

when the blood-pressure was low, but a pure depressor response was quite frequently obtained with a fairly normal blood-pressure.   A depressor action preceded by a slight pressor action was quite commonly
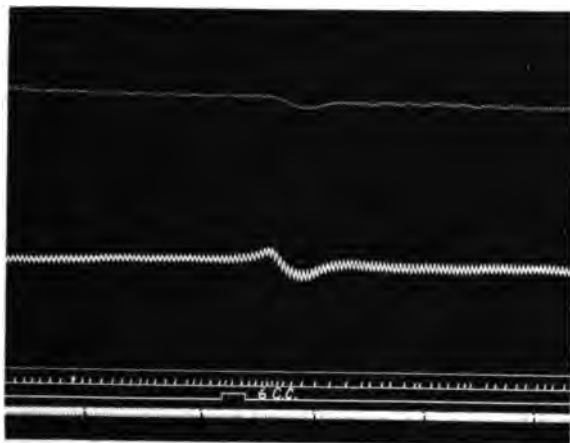
Fig. 121.—Kymograph record of pancreatic volume, blood-pressure, and rate of pancreatic flow.
Each was decreased by the injection of 6 c.c. of 1 : 500,000 adrenalin solution.   Time in minutes and seconds.
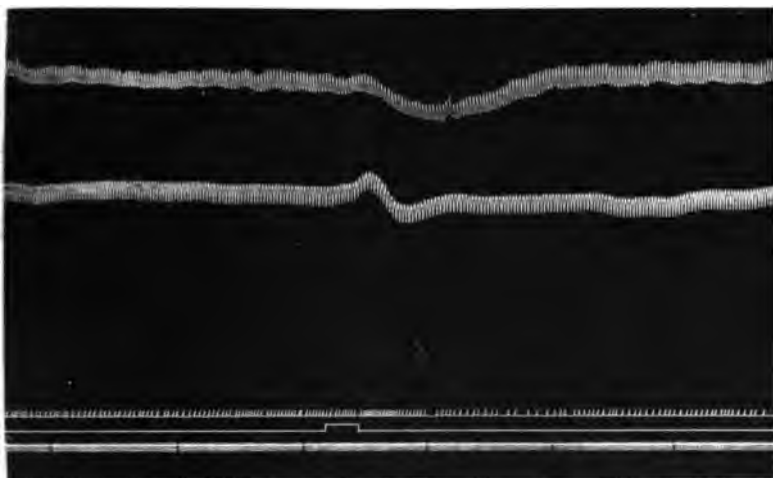
Fig. 122.—Kymograph record of pancreatic volume, blood-pressure, and rate of pancreatic flow.
Each was decreased by the injection of 10 c.c. of 1 : 500,000 adrenalin solution.   Time in minutes and seconds.

secured.   The slight initial rise in blood-pressure was due, at least partially, to the quantity of fluid injected.

The action of relatively large doses of adrenalin, injected intraven-

ously at a rapid rate, on the flow of secretion from an active pancreas is very uniform. As the blood-pressure suddenly increases the pancreatic flow is at first slightly increased for a few seconds, but soon decreases, and it may be completely inhibited. The decrease in pancreatic secretion usually persists a short time after the blood-pressure has reached its previous level, and returns to normal under a continuous injection of secretin. Large doses of adrenalin which increase blood-pressure 50 mm. or more have never failed, in our experiments, to decrease the flow of pancreatic secretion.

Small doses of adrenalin injected slowly, or large amounts of a weak
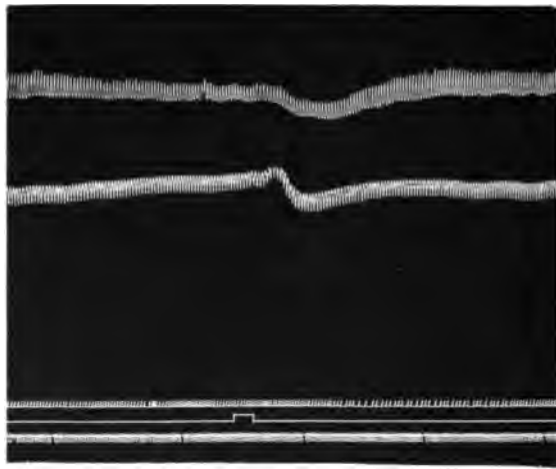
Fig. 123.—Kymograph record of pancreatic volume, blood-pressure, and rate of pancreatic flow. Time in minutes and seconds. Record shows the effect of injection of 10 c.c. of 1 : 500,000 adrenalin solution Pancreatic volume, blood-pressure, and rate of pancreatic flow are all decreased.

solution of the substance injected rapidly, have a variable action on the flow of pancreatic secretion. In a very few animals the pancreatic flow was not affected until a dose sufficient to increase blood-pressure 40 mm. was injected. In other animals the pancreas was so sensitive to the action of adrenalin that it was possible, by injecting a very weak solution quite slowly, to decrease the flow of pancreatic secretion without affecting the general blood-pressure.

When adrenalin produced a depressor action on blood-pressure, it usually also decreased pancreatic flow. In many instances the decrease was quite marked, while in others it was slight.

In none of our experiments did adrenalin increase the rate of secretion.

The decrease in the flow of pancreatic secretion secured by adrenalin is not directly dependent on general blood-pressure.   The fact that by varying the doses and rate of injection of adrenalin it is possible to produce both pressor and depressor response, but only a decrease in pancreatic flow in each instance demonstrates this.   It is also proved by the results of the injection of small doses of adrenalin with a varying general blood-pressure.   When the injection of a small dose of adrenalin decreases the flow of pancreatic juice at the beginning of an experiment when the blood-pressure is relatively high, an equal dose will produce a comparable decrease in flow at the end of the experiment,
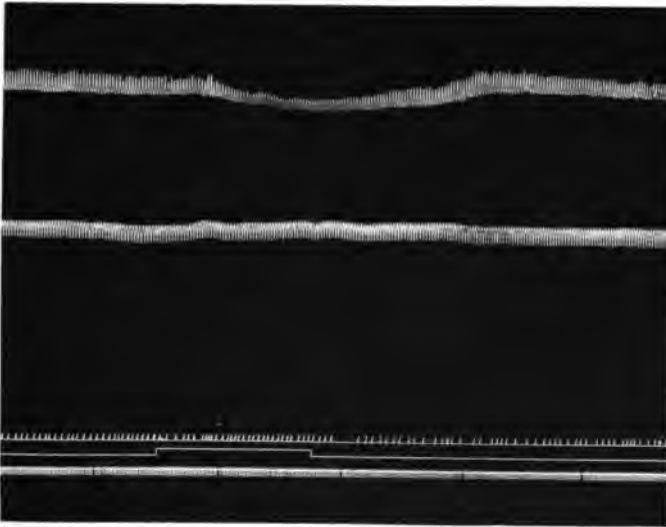
Fig. 124.—Kymograph record of pancreatic volume, blood-pressure, and rate of pancreatic flow. Time in minutes and seconds. Record shows the effect of slowly injecting 10 c.c. of 1 : 500,000 adrenalin solution.   Pancreatic volume decreased; blood-pressure was only very slightly affected; rate of pancreatic flow was noticeably decreased.

when the blood-pressure is low, and the maximum pressure produced may be only half of that produced at the beginning of the experiment.

As Edmunds showed in his work, the probable solution of the problem is secured by a study of pancreatic volume following the injection of adrenalin.   By applying a suitable plethysmograph to the pancreas we were able to obtain several records showing the changes of pancreatic volume due to depressor doses of adrenalin.   We were not always able to obtain a record of volume changes, owing to technical difficulties, but when we did, they always denoted a decrease, namely, a vasoconstriction. Even when adrenalin produced a marked depressor action on general

blood-pressure, the pancreatic volume and the rate of pancreatic flow also decreased.

SUMMARY

Large doses of adrenalin which produce a marked rise of blood-pressure always decrease the flow of pancreatic secretion. Very small doses usually also decrease the activity of the pancreas regardless of whether a pressor or depressor action of blood-pressure is produced. Adrenalin also decreases pancreatic volume at the same time it decreases pancreatic flow, regardless of its effect on the general blood-pressure. The results of these experiments do not allow us to state definitely that adrenalin does not specifically inhibit the action of the pancreatic cells, but it would seem that the action of adrenalin in inhibiting the pancreatic secretion depends on the amount of blood passing through the gland. Large doses of adrenalin, even though general blood-pressure is greatly increased, decrease the amount of blood to the pancreas by excessive local constriction, and thus decrease the flow of pancreatic juice. Small doses may or may not affect the secretion of the pancreas, depending on whether the relation of the local constriction and the changes in general blood-pressure change the amount of blood going to the gland. The pancreatic vessels may constrict with a dose which will produce enough dilatation elsewhere to cause a decrease in general blood-pressure, or which may not produce enough general action to affect blood-pressure at all. In every case the cause is the same—a reduction of the amount of blood passing through the gland per unit of time. However, these results all tend to accentuate the fact that the pancreatic vessels seem to be more sensitive toward the pressor action of adrenalin than those of any other region concerning which we have data.

REFERENCES

1. Bayliss, W. M., and Starling, E. H.: The mechanism of pancreatic secretion. Jour. Physiol., 1902, xxviii, 325–353.
2. Benedicenti, A.: L'action de l'adrenaline sur la secrétion pancreatique. Arch. ital. de biol., 1906, xlv, 1–17.
3. Cannon, W. B., and Lyman, H.: The depressor effect of adrenalin on arterial pressure. Am. Jour. Physiol., 1912–13, xxxi, 376–398.
4. Edmunds, C. W.: The antagonism of the adrenal glands against the pancreas. Jour. Pharmacol. and Exp. Therap., 1909–10, i, 135–150.
5. Edmunds, C. W.: Further study of the relation of adrenals to pancreatic activity. Jour. Pharmacol. and Exp. Therap., 1910–11, ii, 559–574.
6. Hoskins, R. G., and McClure, C. W.: The adrenal glands and blood-pressure. Arch. Int. Med., 1912, x, 343–356.
7. Mann, F. C., and Drips, D.: The relation of the adrenals to the pancreas. Arch. Int. Med., 1915, xvi, 681–692.
8. Pemberton, B., and Sweet, J. E.: The inhibition of pancreatic activity by extracts of suprarenal and pituitary bodies. Arch. Int. Med., 1908, i, 628–647.
9. Pemberton, B., and Sweet, J. E.: Further studies on the influence of the ductless glands on the pancreas. Arch. Int. Med., 1910, v, 466–481.

THE SPLEEN DURING HIBERNATION*

F. C. MANN AND DELLA DRIPS

In a study of the ductless glands during hibernation the other organs were observed routinely.[1] The most striking changes noted in the hibernating animals occurred in the spleen.

Polimanti,[2] in his recent monograph on hibernation, mentions the spleen only briefly, and there are few references in his comprehensive bibliography to observations on the spleen during hibernation. It was thought that a note recording our observations might be of value.

These observations were carried out on spermophiles (S. tridecemlineatus). The data in regard to length of time torpid, temperature, and other important factors of the hibernating animal have been given in detail in another paper[1] and will not be repeated here. Suffice to state that spleens from 30 hibernating animals and a corresponding number from active animals were studied. Of the active animals 12 were killed after varying lengths of time of activity after awakening. This number does not include the animals used in the special experiments reported in this article. The time of hibernation varied from twelve hours to one hundred and seventy-five days. Specimens of the active animals were obtained at various times throughout the year.

Unless otherwise stated, the active animals were killed by bleeding under light anesthesia. The torpid animals were bled without anesthesia. The specimens were fixed in several fluids, those most used being formalin, neutral formalin, Zenker, and Zenker acetic. The sections were stained with hematoxylin eosin, Mallory's connective-tissue stain, and a few other special stains, such as Scharlach R.

The structure of the spleen of the spermophile does not differ essentially from that of the spleen of other rodents. The splenic nodules are prominent and the sinuses rather large. The most notable fact in regard to the histology of the organ is the relatively thick trabeculas con-

taining a large amount of smooth muscle. In the gland of the active animal usually only a small amount of blood is found.

Within twelve hours after an animal becomes torpid the spleen presents a very characteristic appearance. Grossly and microscopically the organ is markedly congested. It is greatly enlarged and much darker in color than normal. The capsule is tense and the tissue friable. On section an increased amount of dark blood escapes. Owing to the large
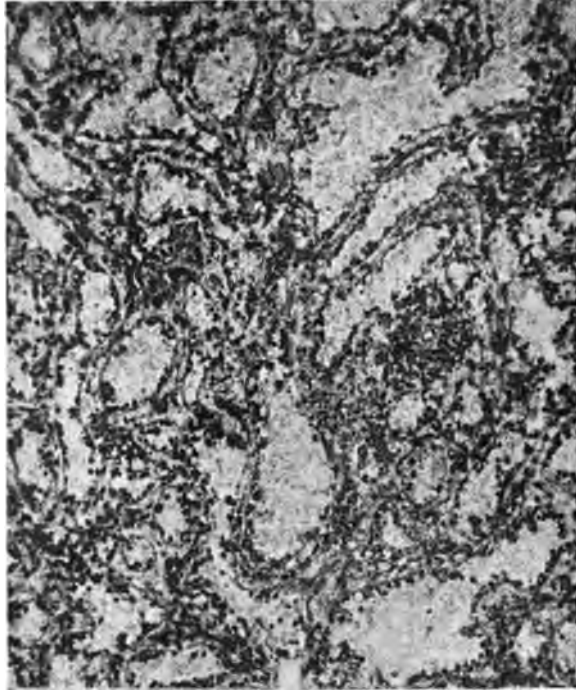
Fig. 125.—Photomicrograph of spleen of Spermophile 260, a female captured in the spring of 1915. It had been torpid continuously for fifteen days, although it had hibernated for a short time also earlier in the season. Did not have access to food. Killed January 1, 1916, by bleeding. At this time it weighed 85 gm. and the rectal temperature was 12 C. The photomicrograph shows the marked distention of the venous sinuses with blood (× 100).

amount of blood present it is impossible to recognize any of the finer details of the organ grossly. Microscopically the organ presents a most intense congestion. The sinuses and venous capillaries are distended to their fullest extent with blood. In some organs red corpuscles were found in the germ centers. It appeared as if the congestion was so great as to force the cells into these centers.

The hibernating spleen reaches its maximum state of congestion

within a few days after the animal becomes torpid and maintains this condition until after about forty days of hibernation. After the animal has been torpid for seventy-five days the amount of blood contained in the spleen is not greatly in excess of that found in the organ of the active animals. The blood seems to begin to decrease at the periphery of the organ first. This is probably due to the fact that the effect of the contraction of the intrinsic muscles is first exerted on the surface of the organ.
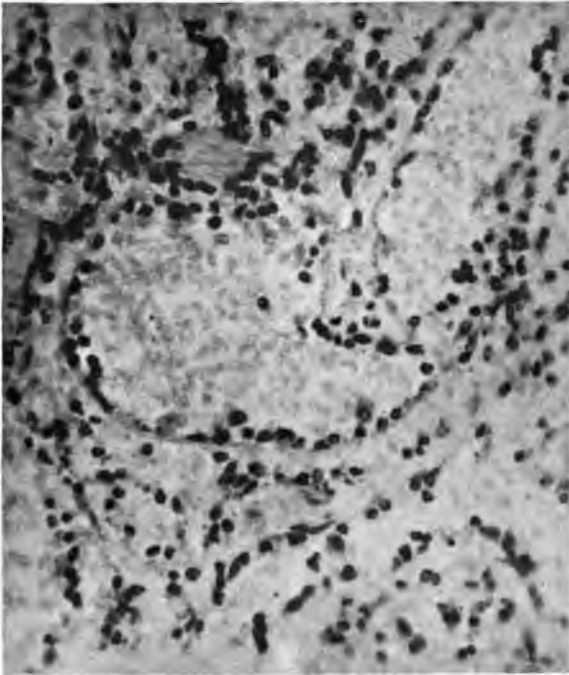
Fig. 126.—Photomicrograph of same section as that shown in Fig. 125 (× 280).

Besides the marked congestion, there seems to be very little other change in the spleen. In some animals which had been torpid for many days there seemed to be a slight proliferation of the connective tissue, especially around the splenic nodules. Specimens of the spleens of both active and torpid animals were fixed in formalin and the section stained with Scharlach R for fat. Rarely were fat droplets found in any of the cells of the organs of active animals. In several of the spleens of torpid animals, certain cells were found containing fat-droplets. These cells, usually few in number, were large lymph-cells which were always found

in the germ centers. We have never observed fat-containing cells in any other part of the spleen.

In the spleen of the active spermophile there can always be found a considerable number of phagocytic endothelial cells containing red blood-corpuscles or blood-pigment. In the congested spleen of the animal which has been torpid for only a short length of time there seems to be a marked decrease in these cells. Owing to the marked congestion,
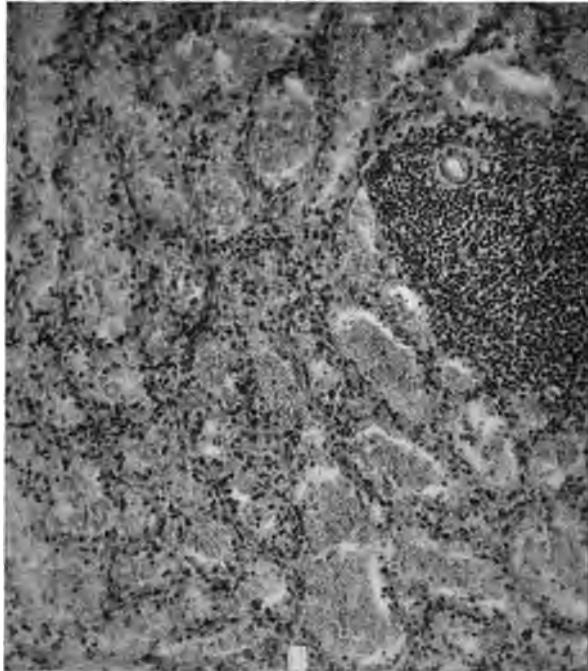
Fig. 127.—Photomicrograph of spleen of Spermophile 117, a male captured in the spring of 1915. It had been torpid for thirty-five days. Had access to food. Killed January 10, 1916, by bleeding. At this time it weighed 165 gm. and the rectal temperature was 14 C.

it may be that this is only a relative decrease or the cells are masked by the large amount of blood present. However, in some of the organs of animals which had been torpid less than forty days we were not able to find any of these cells. They reappeared in the animals which had hibernated longer and were still more numerous in the active animals which were killed within a short period after awakening. However, the largest number have always been found in the active animals.

Some of the torpid animals were killed without bleeding. The con-

gestion of the spleen did not seem to be greater in these animals than in those which were bled.

Some experimental procedures were employed in the attempt to reproduce in the active animal the picture of the spleen found in the torpid animal. Some animals were killed with ether and about fifteen minutes after death the spleen was carefully removed and fixed. Other spermophiles were asphyxiated either in a closed jar or with illuminating
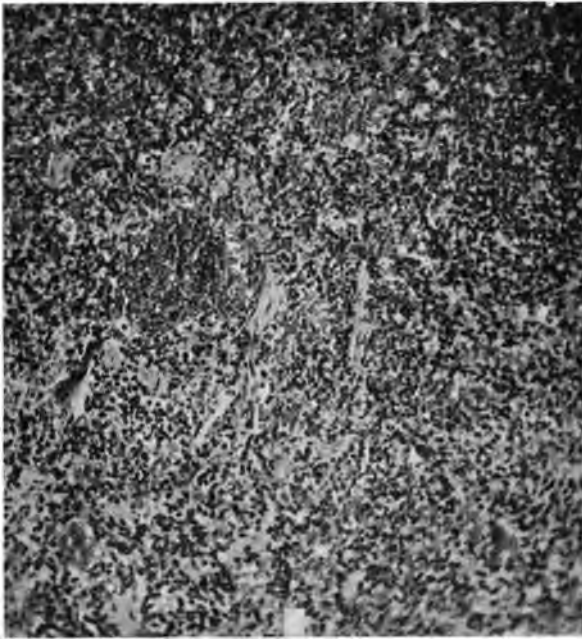
Fig. 128.—Photomicrograph of spleen of Spermophile 266, a female captured in June, 1914. It hibernated when kept in the cold during the winter of 1914–1915. Placed in hibernating room and food withdrawn the latter part of September, 1915. Killed January 27, 1916, after hibernating about one hundred and twenty-five days. Rectal temperature at time of death, 17 C. Daily observations were not made. The spleen is practically normal.

gas. Some animals killed by the latter method were asleep. In some experiments the venous outflow was impeded for a short period before death. While most of the spleens in animals subjected to these experimental procedures showed congestion, it was impossible to attain completely the intense congestion noted in the organ of the animal which had been torpid for only a short time.

The adult spermophile usually withstands operation very well, but removal of the spleen proved to be an exception. Most of the animals

died within a few weeks after splenectomy, but a few lived for several months. Careful observation showed that these splenectomized animals hibernated under the same conditions as the controls.

The intense congestion of the hibernating spleen is probably due to a loss of tone and relaxation of the intrinsic muscles of both the spleen and the blood-vessels. A consideration of the part this plays in the phenomena of hibernation must be purely speculative. It is possible that the spleen acts as a storeroom for the red blood-cells in the early stages of hibernation and allows them to be added to the circulation as needed. The fact that the corpuscles in the congested sinuses appear perfectly normal and that phagocytosis of the red cells seems to be decreased and not increased, as one would anticipate, strengthens this idea. However, the fact that splenectomized animals hibernate normally shows that this is only a secondary factor.

REFERENCES

1. Mann, F. C.: The ductless glands and hibernation. Am. Jour. Physiol., 1916, xli, 173–188.
2. Polimanti, O.: Il letargo. Rome, Bardi, 1913, 683 pp.

THE RELATION OF THE SPLEEN TO CERTAIN OBSCURE CLINICAL PHENOMENA*

W. J. MAYO

There is a fascination about the study of the spleen in its relation to clinical medicine which is increased by the fact that those twin sisters of progress, pathology, and experimental medicine, have contributed so little to our knowledge of the organ. The result has been that what we know and what we think we know about the spleen is largely the result of circumstantial evidence having its origin in comparative anatomy and physiology, and the results of clinical experiences capable of different interpretations. As the spleen has no external secretion and no known internal secretion, the results of its actions cannot be studied directly. We know that the removal of the normal spleen rendered necessary by traumatism, etc., introduces no serious bodily change. In practically all the diseases in which splenectomy is thought to be indicated the spleen is enlarged, and this enlargement, on account of the concealed situation of the organ, must be very considerable, perhaps twice the normal size before we can know that the enlargement exists. Palpation gives the only definite information as to the size of the spleen; if it cannot be felt, percussion is a poor and misleading substitute. Much may be expected from the roentgenogram in the future to make manifest the size and position of the spleen as it has so satisfactorily done with the kidney. We are as yet unable to study the earlier manifestations of associated diseases in relation to the size of the spleen; and its lesions are gross before we can be certain that it is concerned in the production of the symptoms from which the patient suffers. Another source of uncertainty arises from the fact that the spleen alone is seldom responsible for the production of the clinical phenomena. It is more often the agent than the cause of the illness. In the 168 cases in which we have removed the spleen it was surprising how many diverse clinical condi-

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tions were represented and yet how little the pathologic diagnosis varied. No matter how widely the clinical phenomena differed, the spleens on both gross and microscopic examination showed changes varying chiefly in degree; that is, a more or less marked fibrosis, a greater or a smaller amount of degeneration of the blood-vessels and Malpighian bodies, or a hypotrophic or an atrophic spleen pulp. Cell study of fresh splenic tissue by special methods is needed and gives promise of more definite pathologic comparisons.

Accepting then the necessity for securing what knowledge we may from collateral evidence, an investigation of the facts, near-facts, and fancies, taken as a whole, may throw considerable light on the subject.

The spleen is derived from mesoblastic tissue, and is probably concerned largely with filtration of certain substances from the blood and the product of its activities is delivered to the liver through the splenic vein, suggesting at once what clinical experience has shown—its relation to the blood and to the liver. It may perhaps be most aptly compared to the kidney, also derived from mesoblastic structure, and also without true secretion—a filtering organ. Cushny well expresses the modern view that the kidney has no true secretion, but that it filters certain substances from the blood in proportion to the absolute amount in the plasma, so-called no-threshold bodies and other threshold bodies only when their percentage in the plasma exceeds certain values.

The normal spleen weighs 195 grams (Sappey). It has a very scanty nerve supply from the sympathetic system, but it does contain a considerable amount of non-striated muscle-fiber. Keith has demonstrated that the non-striated muscle has the power of originating contractions independent of nerve supply, and exhibits a most primitive form of control. This attribute is shown wherever non-striated muscle is to be found. The intestine, like the heart, has two beats, the first once or twice to the minute, which we call peristalsis; the second, 12 to 20 times to the minute, which acts as the heart of the portal circulation (Mall). The spleen has what might be called a beat which consists of an enlargement following food intake, with a gradual resumption of its normal size after several hours, showing a definite connection with the digestive function, which is indicated again by the fact that its blood supply is from the celiac axis, the same source of supply as that of the derivatives of the foregut, the stomach, the liver, and the pancreas. Elliott and Kanavel have shown that the intramuscular injection of epinephrin contracts the spleen one-third in size.

The blood entering the spleen is peculiar inasmuch as it comes in direct contact with the splenic pulp, the smaller blood-vessels having lost their elastic coats. This renders the spleen fragile and leads readily to traumatic or spontaneous rupture, resulting in intraperitoneal hemorrhage or hematoma within the splenic substance. The latter condition results in cyst, the most common type of tumor of the spleen (Powers). This peculiarity of the blood-vessels also renders the spleen extraordinarily susceptible to the influence of radium, which acts with vigor on the single coated blood-vessels, non-striated muscle, and the nuclei of cells. It may be surmised that the spleen does not possess an internal secretion of importance not only because removal of the normal organ does not disturb the body metabolism, but also because of its extremely limited sympathetic nerve supply. It is to be noted that the organs of primary internal secretion usually act through the sympathetic nervous system. The adrenals and the pituitary are so closely connected with the chromophil system that their union amounts almost to a single organ, half sympathetic and half secretory. Other organs like the thyroid (Plummer, Kendall), gonads, pancreas, etc., which have internal secretion acting to a large extent through the blood-stream, had at one time or still possess an external secretion as well as an internal. The spleen does not properly fall into either of these categories.

On hypothetic grounds it seems probable that the spleen develops certain enzymes which are important to its function, but it is equally evident that the function of the spleen is shared by other lymphoid and adenoid structures in the body, and that on the removal of the organ the function is continued by these collaborating structures (Warthin).

It has been suggested that the spleen is a retrogressing organ. The outstanding factor of a retrogressing organ is diminished blood-supply (Eccles). The blood-supply of the spleen is enormous, and it may be readily seen that a large percentage of the blood of the body passes through the spleen every hour.

Relations of the Spleen to the Blood

The blood may properly be termed a tissue, consisting of erythrocytes, leukocytes, and platelets, in which the plasma is a fluid medium taking the place of intracellular substance. The white blood is the most primitive, derived from the mesenchyme cell. The earliest heart was possibly a lymphatic heart, circulating white blood, which merged later with the venous heart, leaving among other evidence the lymphatic

connection of the thoracic duct with the venous system. Animals which
have only one kind of blood have white blood. The fetal blood is pro-
duced by the lymphoid and adenoid structures of the body, including the
liver and spleen. From this standpoint, leukemia could be considered a
cancer of the blood in which there is an uncalled-for production of func-
tionless white cells, just as carcinoma is due to the unlimited production
of embryonic epithelial cells, and sarcoma of embryonic connective-tissue
cells. The earliest blood discovered in the fetus is the white, and the
red cells are probably derived from the white cells. The spleen loses its
power to produce red blood at birth and the liver at about the fifth fetal
month, but the spleen retains its power for a limited production of white
cells throughout life and assumes the function of the destruction of worn-
out red cells, which is shown by a relative increase in the white cells and
of hematin in the splenic veins over other veins in the body.

When the spleen is removed in certain enlargements, as in hemolytic
icterus, it is found crowded with erythrocytes in various stages of dis-
integration and we know that the specific splenic cells have phagocytic
properties. Robertson and Rous, in a study of the relation of the spleen
to the blood, have come to the conclusion that fragmented erythrocytes
are not only removed there but that fragmentation must take place in
the spleen. Normal fragmentation depends on the natural life of the
erythrocytes, which has been estimated at from ten to fourteen days.
This estimation has been made largely on the assumption that biliary
pigments are derived entirely from the destruction of erythrocytes.
Whipple and Hooper, by a series of careful experiments, throw consider-
able doubt on the view that the biliary pigments have no other origin
than from destroyed erythrocytes, and it is quite probable that the life
of the red cell is much longer than has been estimated. In some of the
anemias, notably hemolytic iceterus, Chauffard and Widal show that the
erythrocytes circulating in the blood are unusually fragile and that this
fragility leads to undue fragmentation and destruction in the spleen.
They point out that the enlargement of the spleen may be a work-
hypertrophy. Krumbhaar believes that the specific hormone of the
spleen is activated by passage through the liver, and by a series of in-
teresting experiments he throws some light on the relation of the spleen
to the blood and to the liver. He shows that there is a certain amount of
anemia after splenectomy and that ligation of the splenic vein does not
cause necrosis. This latter observation has a bearing on the changes in
the spleen incident to thrombosis of the splenic vein. Singular difficul-

ties confront the surgeon in experimental work in his attempts to solve these problems. Not the least of these difficulties is the fact that the experimentation on animals is on the normal spleen.

RELATION OF THE SPLEEN TO THE LIVER

The liver is the great organ of defense. Its extreme importance is shown in the fact that it is one of the few organs which has the power of regeneration. We know that the liver destroys bacteria and protozoa and detoxicates poisons, both biologic and chemical, which are brought to it from the portal circulation. The liver bears the most important relations to bodily metabolism, especially to the formation of sugars from carbohydrates and the development of amino-acids from proteins. It receives through the portal vein all the nutritive material derived from food through the gastromesenteric system, and also the nutritive values in the material which the spleen obtains from the blood.

The diseases of the liver are little understood, and while a vast amount of work has been done, the nature of its metabolic activities is to some extent a matter of conjecture. Among its most important diseases are those which result from the intrahepatic development of connective tissue, causing cirrhosis, a process which may be wide-spread or localized. The cirrhotic liver may be and is enlarged more often than we are led to think because of our more complete understanding of the alcoholic cirrhosis of the Laennec type, the so-called hobnail or gin liver. Yet there is no fundamental difference between the atrophic cirrhosis and the hypertrophic cirrhosis of the beer drinker in which fatty tissue smoothes out the connective-tissue contractions and increases bulk. The cirrhosis secondary to splenic disease, if portal, is of the atrophic or hobnail type, showing that the cause concerns protein, not fat metabolism. In biliary cirrhosis, on the contrary, the liver is always enlarged. Three types of hepatic cirrhosis stand out prominently—the toxic, represented by the alcoholic portal cirrhosis; the protozoal, of which syphilitic cirrhosis is representative, and the bacterial, of which biliary cirrhosis from common-duct infections is a type. In the portal cirrhosis the connective tissue is related to the portal venous system and ascites is an early manifestation, while jaundice is a late one. In biliary cirrhosis the connective tissue is associated with the biliary canals, jaundice is an early manifestation, and ascites a late one. Biliary cirrhosis is even less well understood than the portal type, and there are various subdivisions, such as the pigmentary (hemochromatosis) and the so-called Hanot's

cirrhosis; the latter designation evidently includes cases of hemolytic icterus and serves only still further to confuse the issue.

Nature, in dealing with poisonous substances within the body in a general way, employs two methods: (1) Detoxication and elimination, and (2) encapsulation. Portal cirrhosis may be looked on as failure to detoxicate and eliminate certain diffuse poisons, and eventually there is an attempt at encapsulation of the noxious agents, resulting in the introduction of connective tissue about the portal radicals. The enlargement of the spleen, which so often accompanies portal cirrhosis, suggests that the primary source of these poisons may be in the spleen, and in some cases of portal cirrhosis in which we have removed the enlarged spleen the results justify the presumption. In Banti's syndrome the portal cirrhosis is a late stage of splenic anemia, and even in advanced disease the removal of the spleen often cures, the liver regenerating to a marked degree. In portal cirrhosis supposed to be primary, the spleen may be enlarged to a considerable extent without being manifest until a late stage. Sometimes it is a moot question whether the liver or the spleen was first affected—all going to show how little we know about the whole subject.

The biliary cirrhoses, in many cases at least, have their origin in infections in the common duct, associated with gallstone disease. In such cases the spleen may or may not show great enlargement. In other cases in which no such infection exists in the common duct the spleen may be found to be very large and suggests the possibility that it has carried to the liver toxic materials which have safely passed through the portal side, but have exercised a large influence on the hepatic cells and the smaller bile-ducts. This we know to be the fact in connection with hemolytic icterus, as the removal of the spleen promptly relieves the jaundice. The enlarged liver thus may not be a true biliary cirrhosis, as we had thought, but possibly in part at least an excess of function causing hepatic hypertrophy as well as cirrhosis in the attempt to care for the erythrocytic débris destroyed in the spleen and carried to the liver by the portal vein.

RELATION OF THE SPLEEN TO BACTERIA AND PROTOZOA

Not infrequently living organisms are introduced into the human economy, and such introduction initiates bodily resistance. Vaughan has pointed out that a patient has typhoid during the prodromal period, but that which we call typhoid is nature's defense manifestation. Pre-

ventive serums, such as vaccination for smallpox, typhoid, etc., act to educate the cells of the body to resistance. It is probably true that at times organs such as the tonsils, which permit bacteria to enter the blood-stream, are acting as immunizing agents, allowing the early introduction of a few bacteria which act to cure rather than to cause the disease. Phagocytes may be considered educated defense cells ready to engulf bacteria on contact and perhaps depend on bacteria for their nourish-ment. In typhoid fever the spleen becomes enlarged as a result of its straining function. The accumulated bacteria which have been strained out of the blood are sent to the liver for destruction. A failure in elimi-nation of the bacteria from the spleen to the liver may result in multiple or single abscesses containing pure culture of typhoid bacillus. We have operated in several such cases.

Enlargements of the spleen from chronic sepsis are not uncommon and may act as secondary distributing centers of infections. Focal in-fections in various parts of the body may act as the primary source of the bacterial invasion. Septic endocarditis is a notable example. In eight cases we have removed a very large spleen showing the picture of sepsis—infarcts, etc. This type of chronic splenomegaly is most apt to be confused with splenic anemia.

While tuberculosis of the spleen is considered by some observers as never primary, this condition has occasionally constituted the only known focus in the body, and the removal of such a tuberculous spleen has permanently cured the patient. We have removed the enlarged spleen in three instances for tuberculosis supposed to be primary in the spleen. One patient died within the year from tuberculosis and we must conclude that there were other undiscovered foci. The remaining two patients have recovered and remain well.

Pathogenic protozoa, such as the plasmodium of malaria, the spiro-chete of syphilis, etc., produce chronic splenic enlargements from which it may be extremely difficult to dislodge the organisms. Jonnesco and others have removed the spleen for the ague cake of malaria, but with a high mortality. Newer and better methods of quinin therapy render so radical an operation unnecessary—at least very seldom indicated.

Spirochetal hibernation in the spleen is not unusual, and failure to eradicate the disease by salvarsan and prolonged mercurial treatment may result in a syphilitic spleen which permits not only luetic reinfection of the body, but also causes a high grade of chronic anemia. In four cases of this type removal of the spleen has promptly cured the anemia,

and the lues has thereafter quickly responded to renewed treatment. In all these spleens either spirochetes were found or gummata in spleen or liver were demonstrated, showing again the relation of the spleen to hepatic disease.

A very interesting question comes up in this connection. Must all the blood of the body pass haphazard through the spleen in order that these various materials, bacterial, protozoal, cellular, and toxic, shall be strained out, or is there a definite affinity in the spleen which furnishes an attraction for such elements? Rosenow's splendid experiments showing the specificity of bacteria and their definite attraction for certain organs make it seem probable that some form of chemotaxis attracts to the spleen all these various agents.

The foregoing brief résumé gives prominence to certain data which tend to establish that:

1. Enlargements of the spleen not due to new growths are associated with definite pathologic changes in the blood and the liver.

2. The enlargement of the spleen is often the result of agencies which are not primarily connected with the spleen, and in many cases the splenomegalia is a work-hypertrophy, a secondary, not a primary, cause of the disease with which it is connected.

I have reviewed with some care the results of splenectomy for the relief of certain conditions with the idea of establishing the value of the operation. Dr. H. Z. Giffin, who has taken the utmost interest in the work, has made a number of clinical contributions to the subject, and has aided me in the review.

PERNICIOUS ANEMIA

We have removed the spleen 50 times for pernicious anemia. In each case the diagnosis was well established, and the spleen, with four exceptions, was above normal in weight. In some instances the spleen was greatly enlarged, weighing up to 2330 gm.

There has been no definite relation between the size of the spleen and the seriousness of the disease, nor was there any direct relationship between the result of the splenectomy and the size of the spleen removed. This of itself is a suspicious circumstance. The benefit derived from splenectomy, generally speaking, has followed the removal of a definitely enlarged spleen. The failure to establish such relationship in pernicious anemia, or to connect with the disease such gross and microscopic changes as are to be found in the removed spleens, would lead us to ex-

pect only limited benefit rather than cure of pernicious anemia through splenectomy. There was temporary improvement in every case, but following splenectomy we had some cases in which the cord changes progressed in spite of a great improvement in the anemia. We have not had a patient who has been cured, but all in all, in about 75 per cent of the cases, the benefit might be said to be sufficient to justify the operation. In the total number of operations three patients in our early experience died from the operation; the hemoglobin was under 30 per cent, the red cells were under a million. These patients should have been transfused before operation. Since practising transfusion in advance of splenectomy, when the blood has seriously deteriorated, we have had no deaths. There were no operative deaths in the last 32 cases. In many cases after initial improvement by transfusion and splenectomy, relapse has taken place, followed again by improvement after transfusion. We have carried some of these patients along for months in fair health by repeated transfusions; as many as thirty have been given to a single patient. Following each transfusion there would be marked benefit, with gradual depreciation, until transfusion again became necessary. It has been believed that the introduction of new blood stimulates the hematopoietic organs, and this is probably the true hypothesis in patients whose bone-marrow is not too severely damaged. Yet it should be noted that immediately after the transfusion, in certain cases, the anemia is relieved, the hemoglobin brought up from 10 to 30 points, and the red cells advanced appreciably, only to be followed by a gradual decline. These are the predominantly myelotoxic types. It is an interesting conjecture whether or not the patient may live on the work of transfused blood as well as be stimulated to the formation of new blood. A probable explanation is that the life of the red corpuscles is much longer than we have thought, and that the anemia returns in proportion as this fresh aid is used up. The significant blood changes in pernicious anemia that differentiate it from secondary anemias are the changes in the number and type of the red corpuscles and in the blast cells found in the blood. The blast cells are the mothers of the erythrocytes, and each blast cell thrown into the blood represents a permanent loss of blood-making power. Therefore, neither stimulation nor treatment can reproduce that which has been lost. The difficulty with the whole subject of pernicious anemia concerns the fact that we do not recognize the disease until such vital and permanent changes as are indicated in the actual loss of these blast cells have taken place. It is

even possible that pernicious anemia, in its beginning, is not a definite
entity, but that it is a terminal change of several conditions which we
have not recognized until they have reached the final stage.   Clinically,
however, it is a very definite disease when both history and blood picture
are developed.   Pernicious anemia may be called a cancer of the red
cells, recognized in the hopeless stage.   When the early histories of
patients with pernicious anemia are studied, the symptomatology seems
fairly clear; yet many patients are seen with anemias which are sus-
pected to be pernicious but which never develop the true characteristics
of the disease.   If pernicious anemia is to be cured, it must be done be-
fore permanent damage to the hematopoietic organs has taken place.
It is possible that certain types may be cured; yet so firmly fixed is our
belief concerning the incurability of the disease that should we have
patients cured by splenectomy we would be inclined to lift them out of
the category of pernicious anemia and to group them with either hemo-
lytic icterus or splenic anemia.

To sum up, splenectomy has a field of usefulness in selected cases of
pernicious anemia, especially in those showing a marked hemolysis by
the Schneider duodenal test and evidence of slight bone-marrow damage.
The operation of removal of the spleen for pernicious anemia is not, as a
rule, difficult.   The spleen is only of moderate size, and not very ad-
herent.

LEUKEMIA

If there has been any one condition believed to be non-surgical and
incurable, it is splenomyelogenous leukemia.   The theory has been that
95 per cent at least of such patients operated on would die as a result of
the operation, and that the 5 per cent who lived would not be benefited.
Yet we have long known therapeutic agents (benzol, x-ray, etc.) which
would reduce the size of the spleen and would also improve the condition
of the blood; and as the size of the spleen became reduced, such improve-
ment might be expected.   With the use of radium, which could be read-
ily applied over the area of the spleen, a vast change came about in the
therapeusis of splenomyelogenous leukemia.   I do not know of any
clinical experience that is more striking than the result which follows the
application of radium over a huge leukemic spleen.   Many times the
spleen shrinks so greatly as to disappear below the left costal margin,
the white blood-corpuscles drop from hundreds of thousands to under
10,000.   I have seen a leukopenia produced, the white cells dropping
from 600,000 to 3,700 in five weeks.   Accompanying this extraordinary

reduction in the size of the spleen and reduction in the number of white cells an equally extraordinary improvement in the anemia takes place, and the patient is marvelously benefited.   As the spleen gradually increases again in size the white cells increase, the red cells decrease, and the patient loses ground.   It is well to eliminate all our presumptions concerning this disease and pause for a moment in perspective.   Reduce the size of the leukemic spleen, and synchronously the white cells go down, the red cells come up, and the patient improves.   As the spleen enlarges the whites come up, the reds come down, and the patient goes down.   Have we in this, as in so many other instances, allowed tradition to hamper progress?

My first experience in splenectomy for myelogenous leukemia was with a patient who came to the Clinic with a greatly enlarged spleen, a white count of between 200,000 and 300,000, and who gave a history of having had the disease for two years.   There had been very great improvement under x-ray therapy; at one time the white cells were reduced by it to a point under 50,000, but, as regularly happens, the x-ray had finally lost its effect, and the patient's condition when examined was worse than it had been at any former time.   The patient herself was greatly impressed with the definite connection between her condition and the size of the spleen, and was anxious to have it removed.   I removed the organ, and the patient made an excellent surgical recovery. Within ten days the white-cell count had dropped to less than 50,000 and the patient is greatly improved now, more than one year after the splenectomy.

Based on this experience we have, in a number of instances, reduced the size of the spleen with radium until the blood count approximated the normal, and then removed the spleen.   We have found it inadvisable to force an extreme reduction of the leukocytes before splenectomy. If the general condition of the patient is good, a leukocyte count of 30,000 or less is satisfactory.   All the patients save two have been markedly relieved.   In the 19 cases there were no operative deaths. That these patients are cured I cannot believe, but the experience has been interesting and suggestive.

Here again we find ourselves in difficulties not dissimilar to those in connection with the etiology and clinical course of pernicious anemia. One patient in our earlier experience, I remember well, had been treated for leukemia during a period of five months in a large and well-known hospital, and in another for three months.   We diagnosed the condition

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as splenic anemia. The spleen was removed, the patient promptly recovered, and has remained well now for more than five years. It is possible that we recognize leukemia as a disease only after it has reached the hopeless stage, a terminal condition of a much more common though unrecognized malady. It is questionable whether all the cases of splenomyelogenous leukemia advance to the point where they are recognized as leukemia. These are interesting problems which cannot now be answered. Leukemia may be called a cancer of the white blood, recognized in the hopeless stage. The leukemic spleen is not adherent, as a rule, and after reduction in size by radium is readily removed.

Hemolytic Icterus

We have performed splenectomy 19 times for hemolytic icterus. The results have been astonishingly good. I do not know of an operation giving more gratifying results. The jaundice which the patient has had for perhaps years will be perceptibly less in forty-eight hours, and within four days will have quite disappeared. Sixty per cent of these patients have complicating gallstones, apparently due to the greatly thickened bile, the result of pigments derived from the disintegrated erythrocytes. There are two types of hemolytic icterus, the familial or congenital type of Minkowski and the acquired type of Hayem and Widal. In the familial type several members of the same family may be affected, and possibly it may be found through several generations. As a rule, it is less serious than the acquired variety. Although never robust, many times those affected with familial hemolytic icterus will live out a normal life expectancy. The acquired type is much more serious, and ends, as a rule, in death from some intercurrent malady after years of chronic semi-invalidism.

The outstanding features of hemolytic icterus are the enlarged spleen, the more or less enlarged liver, and chronic recurring jaundice, without gross obstruction in the bile-ducts. Bile is always to be found in the stool. Inasmuch as a high percentage of these patients have complicating gallstones, they may have an increase of jaundice due to a secondary infection from gallstones, varying the syndrome and introducing diagnostic difficulties. These patients all show marked anemia, and usually crises more or less serious develop in which there is pain over the region of the liver and spleen, with malaise, some increase of temperature, and an increase of jaundice. Chauffard and Widal have pointed out the diagnostic phenomena of increased fragility of the erythrocyte, which

is practically constant. Splenectomy, as a rule, is not difficult in these cases, for although the spleen may be quite large it is seldom adherent to a marked degree. There was but one operative death in our series. This patient was operated on during a crisis, and death probably would not have occurred had the operation been performed in the interval between crises.

Biliary Cirrhosis

Hemolytic jaundice is often confused with certain types of non-infective biliary cirrhosis, and especially with the so-called Hanot's cirrhosis. We have removed the spleen four times for biliary cirrhosis, which could not be properly classified as hemolytic jaundice. All the patients were above thirty years of age. Were it not for the age, the cases could be called Hanot's cirrhosis. The results in three were very satisfactory. The jaundice disappeared to a large extent, and the patients were able to return to work; but in all the liver remained large. The operation of splenectomy for biliary cirrhosis is somewhat trouble-some and difficult—more so than in hemolytic icterus. In our cases the spleen was large and there were many adhesions. In two the liver was sufficiently large to interfere mechanically with the operation.

Splenic Anemia

Osler was one of the first to describe splenic anemia, and his classic contributions, coming as they did at an early time, created a great and lasting interest in the condition. Splenic anemia is at least a clinical entity, but has been confused with many varieties of splenomegalias, syphilitic, septic, malarial, hemolytic jaundice, pernicious anemia, etc. Little by little an irreducible minimum is being reached and a definite type established. The patients having large spleens develop a pro-gressive anemia and cirrhosis of the liver as a terminal condition to which Banti's name has been given.

The course of splenic anemia is chronic. There may be intervals of years in which the patient enjoys a fair degree of health, but eventually it leads to a fatal issue, the debilitated patients succumbing to inter-current disease.

Hemorrhages from the stomach are of frequent occurrence in splenic anemia, and sometimes hemorrhage is the first symptom that may be noted. The hemorrhages are probably gastrotoxic in origin, and while, as a rule, fatal hemorrhage does not result, frequent, recurring hemor-

rhages cause great debility. The gastric hemorrhage of splenic anemia is a symptom well worthy of attention. It is not different from that which occurs in connection with hepatic cirrhosis, and it is altogether probable that many of the unexplained hemorrhages from the stomach in which no local lesion of the gastric mucosa is to be found are a result of the toxic condition which precedes, accompanies, or is caused by splenic anemia and cirrhosis of the liver. Balfour, in a paper on the causes of gastric hemorrhage, calls special attention to the relationship of the spleen and liver to the bleeding. In gastric hemorrhage we must think of the spleen and the liver as causative factors, just as in the differentiation of the causes of jaundice the spleen must be thought of as well as the liver. Warthin and others have found that many cases of splenic anemia show thrombosis of the splenic vein after death, and they believe that the thrombosis is the cause of the splenic condition. In one of our patients who died the cause of death was found to be due to long-standing splenic and portal thrombosis. The final catastrophe was brought about by thrombosis of the superior mesenteric vein. It may be contended that splenomegaly associated with splenic, portal, or mesenteric thrombosis (one or all) would be better grouped with infectious splenomegaly (probably streptococcal) rather than with true splenic anemia.

The pseudoleukemia of infants described by von Jaksch is closely associated, if not identical, with splenic anemia, but because of the hematopoietic variability of infancy is often accompanied by a high white cell count. Such cases are usually to be relieved by dietetic management, but the spleen has been removed with prompt and striking improvement. Balfour splenectomized a two and a half year old child presenting the complete picture of splenic anemia.

Splenic anemia is cured by splenectomy in a high percentage of cases, and it should be performed before portal cirrhosis or thrombosis of the splenic vein occurs. The spleen is usually large and, as a rule, extremely adherent, and the operation is more difficult and dangerous than in any of the various other diseases for which splenectomy is indicated. In 43 splenectomies for splenic anemia we have lost 4 patients.

Clinically, patients with enlargements of the spleen are to be seen in whom the enlargement is apparently not producing symptoms, but these cases should be looked on as incipient splenic anemia. Such causeless splenomegalias as I have had opportunity to observe have eventually led to marked secondary anemia, although perhaps for years

showing little effect on the patient's health.   I have seen no good and much harm come from chronic splenomegalia, and, other things being equal, such spleens should be removed on general principles.

PORTAL CIRRHOSIS

The portal cirrhosis of the liver which so frequently accompanies the later stages of splenic anemia has led us to remove the spleen in 5 cases of primary portal cirrhosis in which there was enlargement of the spleen. The results on the whole have been gratifying, although one patient died following the operation.   The remaining four are in satisfactory condition.   For those portal cirrhoses with enlarged spleen which occur especially in young adults without alcoholic history, splenectomy would appear to be indicated.   As a matter of fact in cases of this description do we not classify as primary portal cirrhosis those in which the liver condition is discovered first?   If the splenic enlargement is first observed, we call it splenic anemia with portal cirrhosis.

The technic of splenectomy I will not dwell on.   Those who are interested I would refer to the article by Balfour, "The Technique of Splenectomy."

BIBLIOGRAPHY

1. Balfour, D. C.: Splenectomy for repeated gastro-intestinal hemorrhages.   Ann. Surg., 1917, lxv, 89–94.
   The Technique of Splenectomy.   Surg., Gynec. and Obst., 1916, xxiii, 1–6.
2. Chauffard, A.: Pathogénie de l'ictère congénital de l'adulte.   Sem. méd., 1907, xxvii, 25–29.
   Les ictères hémolytiques, ibid., 1908, xxviii, 49–52.
   Cholélithiase pigmentaire dans un cas d'ictère congénital hémolytique; analyse chémique des calculs.   Bull. et mém. Soc. méd. d. hôp. de Par., 1912, xxxiv, 80.
3. Cushny, A. R.: The secretion of urine.   Lond., Longmans, 1917, 241 p.
4. Eccles, R. G.: The tonsils and the struggle for existence.   Medical Record, 1915, lxxxviii, 47–56.
5. Elliott, C. A., and Kanavel, A. B.: Splenectomy for hemolytic icterus.   Surg., Gynec. and Obst., 1915, xxi, 21–37.
6. Giffin, H. Z.: Splenectomy for splenic anemia in childhood and for the splenic anemia of infancy.   Ann. Surg., 1915, lxii, 679–687.
   The treatment by splenectomy of splenomegaly with anemia associated with syphilis.   Am. Jour. Med. Sc., 1916, clii, 5–16.
   A report on the treatment of pernicious anemia by transfusion and splenectomy.   Jour. Am. Med. Assn., 1917, lxviii, 429–432.
   Hemolytic jaundice: A review of seventeen cases.   Surg., Gynec. and Obst., 1917, xxv, 152–161.
   Observations on the treatment of myelocytic leukemia by radium.   Boston Med. and Surg. Jour., 1917, clxxvii, 686–691.
7. Hanot, V.: Étude sur une forme de cirrhose hypertrophique du foie (cirrhose hypertrophique avec ictère chronique).   Paris, 1875, 155 p.
8. Hayem, G.: Variété particulière d'ictère infectieux chronique splenomégalique.   Presse méd., 1898, i, 121–125.
   Nouvelle contribution a l'ictère infectieux chronique splenomégalique.   Bull. et mém. Soc. méd. d. hôp. de Par., 1908, xxv, 122.
   Quoted by Krumbhaar, E. B.: A classification and analysis of clinical types of splenomegaly accompanied by anemia.   Am. Jour. Med. Sc., 1915, cli, 227–245.

9. Jonnesco, T.: Splenectomie pour hypertrophie malarique. Bull. et mém. Soc. de chir. de Bucarest, 1901–1902, iv, 58.
10. Keith, A.: A new theory of the causation of enterostasis. Lancet, 1915, ii, 371–375.
11. Krumbhaar, E. B., Musser, J. H., Jr., and Peet, M. M.: Changes in the blood following diversion of the splenic blood from the liver. A control study of the effects of splenectomy. Jour. Exper. Med., 1916, xxiii, 87–95.
12. Mall, F.: A study of intestinal contraction. Johns Hopkins Hosp. Repts., 1896, i, 37–75.
13. Minkowski: Über einem hereditärischen, unter dem Bild eines chronischen Icterus mit Urobilinurie, Splenomegalie, und Nierensiderosis verlaufende Affection. Verhandl. d. deut. Cong. f. inn. Med., 1900, xviii, 316.
14. Osler, W.: On splenic anemia. Am. Jour. Med. Sc., 1900, cxix, 54–73.
15. Powers, C. A.: Non-parasitic cysts of the spleen. Ann. Surg., 1906, xliii, 48–60.
16. Rosenow, E. C.: Elective localization of streptococci. Jour. Am. Med. Assn., 1915, lxv, 1687–1691.
   Elective localization of bacteria in diseases of the nervous system. Jour. Am. Med. Assn., 1916, lxvii, 662–665.
17. Rous, Peyton, and Robertson, O. H.: The normal fate of erythrocytes. Jour. Exper. Med., 1917, xxv, 651–663; 664–673.
18. Vaughan, V. C.: Infection and immunity. Jour. Am. Med. Assn., 1915, p. 164.
19. Warthin, A. S.: The changes produced in the hemolymph glands of the sheep and goat by splenectomy. Contrib. Med. Research (Vaughan), Ann Arbor, 1903, 216–236.
20. Whipple, G. H., and Hooper, C. W.: Bile pigment metabolism. Am. Jour. Physiol., 1916, xl, 332, 348; 349–359; 1917, xlii, 256–263; 264–279; 544–557.
21. Widal, F., Abrami, P., and Brule, M.: Differenciation de plusieurs types d'ictères hémolytiques. Presse méd., 1907, xv, 641–644. Quoted by Elliott and Kanavel, loc. cit.

SURGERY OF THE SPLEEN*

D. C. BALFOUR

The spleen is unique in that it is a prominent and predominating factor in a very large number of blood dyscrasias and other pathologic processes and clinical entities. Its extensive rôle has produced during the past decade a most voluminous literature. In reviewing this literature, it was found necessary to omit detailed reference to many isolated case reports, which though valuable from a statistical standpoint, were not essential to the purpose of this review.

Historically, splenic surgery is of unusual interest (Krumbhaar,[78] Carstens, and others). The statement has been repeatedly made that in ancient times the spleen was removed from athletes to improve their running, and although this may be doubted, Krumbhaar states that Aristotle suspected that the spleen was not indispensable to life. There seems at least to be no doubt that the spleen was successfully removed from dogs and other animals as early as 1500, and it was common knowledge at that time that animals would live in good condition following removal of the organ. Zaccarelli in 1549 claimed to have removed a spleen from a patient with satisfactory results, but most writers of that period do not credit the story. Well-authenticated cases, however, are recorded in the seventeenth century (Clarke, Matthia). Browne in 1814 reported probably the earliest splenectomy in this country and the patient was living in good health several months later. From that time splenectomy has been performed with increasing frequency, but until the last decade any intelligent classification of the conditions which called for splenectomy had not been possible. One must admire the courage and the progressive spirit of those who, before methods of determining the blood-picture were known, and in spite of the prevailing opinion that the operation was justified only in cases of serious injury with prolapse of the organ, performed splenectomies in patients with splenomegaly and constitutional disturbances (Quittenbaum, Spencer

Wells,[127] and others). The surgery of the spleen was tremendously stimulated by the epoch-making communication of Banti[9] in 1894 describing the disease which bears his name. Splenectomy has been at one time or other advocated in a wide variety of diseases and conditions and it will be necessary for the specific purpose of this review to classify these conditions as follows:

1. Anatomic anomalies and injuries:
    (a) Malposition and malformation.
    (b) Traumatism.
    (c) Accessory spleens.
2. Tumors, cysts, etc., and new-growths:
    (a) Abscess.
    (b) Angioma.
    (c) Cysts:
        (1) Simple.
        (2) Dermoid.
        (3) Hydatid.
    (d) Sarcoma and carcinoma.
3. Chronic splenomegaly occurring in diseases of bacterial or protozoan origin:
    (a) Tuberculosis.
    (b) Syphilis.
    (c) Malaria.
4. Diseases in which the spleen has been proved to be the controlling etiologic factor:
    (a) Splenic anemia:
        Adults.
        Children.
    (b) Hemolytic jaundice:
        Congenital and familial.
        Acquired.
5. Conditions with which the spleen is intimately associated primarily or secondarily:
    (a) Hepatic cirrhosis.
    (b) Gastro-intestinal hemorrhage of unknown cause.
    (c) Thrombophlebitis of splenic and portal veins.
6. Primary endothelioma of the spleen.
    (a) Gaucher's disease.
7. Diseases of the blood and the blood-forming organs:
    (a) Pernicious anemia.
    (b) Splenomedullary leukemia.
8. Unclassified splenomegaly:
    (a) Idiopathic splenomegaly.
    (b) Chronic septic spleen.
    (c) Splenomegaly with eosinophilia.
    (d) Tropical splenomegaly.

MALPOSITION, MALFORMATION, AND TRAUMATISM

Malposition and traumatism have been, during modern times, the indications for the only operative procedures other than splenectomy in surgery of the spleen, although Mayo[88] and Troell have suggested the possible value of ligation of the splenic vessels as a substitute for splenectomy in other than these conditions. Efforts have been made, for example, to relieve the symptoms produced by very mobile spleens by ligating the splenic pedicle (Lanz[82]), although in the majority of such

cases splenectomy has been chosen. McDonald and Mackay reported acute torsion of the pedicle of a movable spleen requiring urgent operation for the relief of the symptoms. In many cases of left-sided diaphragmatic hernia the spleen is to be found in the cavity of the chest and in chronic cases is often firmly adherent (LeConte, Green, Balfour[5]).

It is important to remember that a movable spleen can be and has been mistaken for almost every other type of pelvic, abdominal, and kidney tumor, and vice versa.

In traumatism there has been a choice, depending upon the extent of the injury, between tamponage, suture, splenectomy, or exploration only, if the hemorrhage has ceased. Some important observations have been made during the present war as to the seriousness of injuries to the spleen. Webb and Milligan state that, although splenectomy has been looked upon as an operation of high risk in connection with gunshot wounds of the spleen, their own experience in some 20 cases in which the mortality was 75 per cent showed that death occurred in those cases in which other organs than the spleen were also injured and that in their cases of injured spleen alone the rate of recovery was very high. The frequency with which the spleen was injured, in the experience of Wallace, was 54 times in 965 abdominal operations. In 32 instances it was the only organ injured. The mortality in this group was 50 per cent in uncomplicated cases; 63 per cent in complicated cases. He recommends excision only if the organ is totally disrupted or the vessels torn. If hemorrhage has ceased, it is better to leave the organ alone.

Many cases of spontaneous rupture have been reported. Cannaday quotes Senator and Litten as saying that the chief causes are trauma and malaria, but the accident may occur also in typhus, typhoid, infarcts, pregnancy, hemophilia, and tuberculosis. Willis quotes Johnson and Berger as giving the operative mortality as 25 per cent and the non-operative as 90 per cent. He cites Johnson and Fauntleroy as mentioning pain in the left shoulder as a diagnostic point.

Malformation is of anatomic interest only.

ACCESSORY SPLEENS

Accessory spleens have a very minor importance surgically, although Alexander and Romanes report an accessory spleen causing acute abdominal pain due to torsion of the omentum. The fact that accessory spleens are frequently present (11 per cent of all necropsies, Adami and Nicholls) and that they undergo enlargement after splenectomy has

been performed, perhaps attaches some importance to them as regards their influence in the permanency of results obtained by splenectomy.

Abscess

The occurrence of splenic abscess is not extremely rare. Dege, in 1906, collected about 80 cases. Elting, in a recent review of the subject, shows that the majority of cases occur as a sequence to acute infections, such as typhoid, malaria, dysentery, abscess of the appendix, salpingitis, etc. A few cases apparently have followed trauma, and direct extension from perforation of the stomach, or subphrenic abscess.

Various pyogenic bacteria have been isolated. Kuettner experimentally produced abscesses in spleens of animals by injection of bacteria and oil into the splenic artery, into the substance of the spleen, and by traumatizing splenic pulp without breaking the capsule. Elting states that the greater number probably result from infarcts.

The symptomatology depends on the location of the abscess. The spleen is usually enlarged. An abscess centrally located probably will not be associated with distinctive symptoms. If the abscess is near the capsule, however, pain may be present, either spontaneous or on palpation. The fluoroscope may demonstrate restricted motion or high position of the diaphragm. There may be an associated pleurisy. Fever is not constant. Federmann reports a case with subnormal temperature. Chills occur in many cases, and a leukocytosis of 20,000 to 50,000 is usual. Edema is seen over lower intercostal spaces in some cases. The diagnosis usually can be established by aspiration, from which, Elting states, no bad effects have occurred.

The treatment in the majority of cases has been splenotomy and splenectomy. Elting describes three routes by which splenotomy may be carried out: (1) Transpleural (for abscess of the upper pole associated with subphrenic abscess), by resection of the ninth, tenth, and eleventh ribs in the posterior axillary line; (2) abdominal; and (3) retroperitoneal.

Prognosis without operation is bad (Federmann). However, Doebbelin states that small splenic abscesses are absorbed. In 27 operated cases there were 4 deaths—15 per cent.

Cysts of the Spleen

In 1829 Andral first described a case of cystic disease of the spleen. The incidence of the condition may be judged from the fact that Bircher in 1908 collected in all 54 cases, 21 of which were found at necropsy.

Cysts of the spleen are usually classified as: (1) Echinococcus; (2) dermoid; and (3) simple.

Bryan and Fowler, and Sherren, quoting Thomas, place the occurrence of echinococcus cysts of the spleen at about 2 per cent of all cases of echinococcus infection. Splenectomy is indicated, and the hooklets and scolices can be demonstrated in the cyst cavity. Finkelstein in 1914 reported 3 cases, in 2 of which splenectomy was performed.

Dermoid cysts of the spleen are exceedingly rare.

Simple cysts may be serous, hemorrhagic, or lymphatic (Bircher), and the result of trauma or occlusion of arterioles from amyloid change and ultimate softening of the parenchyma (Boettcher). They are more frequently found in women (24 in 38 cases). Lymphatic cysts are usually multiple and remain small. Hemorrhagic cysts are usually single and large. Langhans, Dowd, and others have described angioma of the spleen, Langhans' case being of the pulsating type, and Dowd's of the cavernous type. Boeckelmann described a case of mixed blood and lymphangiomatous spleen in a child of fifteen months, in which excision was performed. Hemangioma with later a malignant sarcoma-like growth has been reported by Homans, Theile, and others. In 1906 Powers reviewed 31 cases of non-parasitic cysts of the spleen collected from the literature and reported one of his own.

Small cysts give no symptoms. In cases of large cysts the spleen is large; in some instances there are sudden pain and fluctuation, and pronounced friction-rub has been noted. A preoperative diagnosis has rarely been made. Splenectomy has proved the best operative procedure, although puncture, splenotomy, and cystectomy also have been employed. Bircher gives the operative results in 33 cases as follows: (1) Puncture (by cautery), 6 cases, 2 deaths; (2) incision and drainage, marsupialization, 9 cases, 1 death (sepsis); (3) resection of cyst, 4 cases, 1 death (ileus); and (4) splenectomy, 15 cases, no deaths.

SARCOMA AND CARCINOMA OF THE SPLEEN

Jepson and Albert, in 1904, collected 31 cases of primary sarcoma of the spleen and reported the recovery of a girl of fifteen following splenectomy for a nodular sarcomatous enlargement of the spleen. Council in 1912 collected 4 other cases and added one of his own. The types of sarcoma which have been recognized are: (1) Fibrosarcoma; (2) lymphosarcoma; (3) small round-cell sarcoma; and (4) endothelial-cell sarcoma. There are no characteristic symptoms of primary sarcoma

of the spleen. Pain has been reported by some authors, and a nodular, solid tumor is the most significant sign. There are no blood changes of value. The increase in the size of the spleen may be very slow.

The only treatment is splenectomy. Deaver, Bush, and others have referred to the bad prognosis, but apparently well-authenticated cases of primary sarcoma of the spleen permanently cured by splenectomy have been reported.

Carcinoma of the spleen (primary) is much more rare in occurrence even than primary sarcoma; in fact, Bush states that most writers agree that there never has been a convincing case of primary carcinoma of the spleen reported. Smith described a case of metastatic colloid carcinoma of the spleen secondary to malignant papillomatous ovarian cyst removed previously. No other evidence of metastasis could be determined at the time of splenectomy, but the patient died a few months later from general carcinomatosis. The rarity also of secondary carcinoma of the spleen has been the subject of much speculation. Chalatow thinks the protective mechanism of the spleen is not due to anatomic or physiologic factors but to ferments in the spleen. As Hollister pointed out, in advanced malignancy the spleen is usually atrophic, and this, in conjunction with the fact that all infectious processes are associated with more or less enlargement of the spleen, argues against the infectious nature of cancer.

TUBERCULOSIS OF THE SPLEEN

The existence of tuberculosis of the spleen without active tuberculous foci elsewhere in the body has been doubted, Bland-Sutton, for example, believing that splenic tuberculosis is always secondary. Mayo,[88] Halpenny, and Franke, however, have reported cases in which clinical examination could detect no other foci, and in such cases the condition could be spoken of as primary in the spleen. The spleen is frequently involved in children dying of tuberculosis. Hamann, in a collection of 428 cases of tuberculosis in children, found the spleen involved in 66 per cent, while in a large series of cases of tuberculosis in adults splenic tuberculosis was shown in 19 per cent. Winternitz in 1912 collected 51 cases of splenectomy for primary splenic tuberculosis. Coley in 1848 reported the first case of tuberculosis of the spleen found at necropsy, and Monerret in 1859 reported another. Burke in 1889 was the first to remove the spleen for splenic tuberculosis.

An absolute diagnosis of splenic tuberculosis can rarely be made in

the absence of a clear history of an active tuberculous infection elsewhere, although Rendu and Widal in 1899 presented what they believed to be a syndrome characteristic of the disease, in which polycythemia without leukemia and cyanosis was the predominating feature. Douglas and Eisenbrey confirm the observations of Rendu and Widal, citing the case of a man with a red-cell count of 8,800,000 in which the diagnosis was confirmed by operation. This observation has not had general confirmation, however, and in the cases which have come to operation in the Mayo Clinic polycythemia has not been present. A diagnosis of splenic tuberculosis can be justifiably assumed in the case of a patient with an otherwise unexplained chronic splenomegaly, who has a quiescent or active pulmonary tuberculosis. Pain over the enlarged spleen may be of some significance in such cases. I recently removed a tuberculous spleen from a patient in whom upper abdominal pain, chiefly in the left hypochondrium, was a very marked symptom, and was explained by the operative findings of most extensive adhesions which completely encapsulated the spleen.

Syphilitic Splenomegaly

Splenomegaly is not an uncommon occurrence in early syphilis. In children, particularly, syphilitic splenomegaly is common, Carpenter showing that syphilis is second only to rickets as a cause of splenomegaly in infancy. Gummatous affection of the spleen is rare both in children and adults (Still).

Splenectomy has been performed in only a few recorded instances of syphilitic splenomegaly, but the results have been conclusive evidence that not only may syphilitic splenomegaly occasionally resist the most advanced antisyphilitic treatment, but the disease may be eradicated and the blood-picture brought to normal by splenectomy (Coupland, Hartwell, French and Turner, and Giffin[55]). Up to July, 1916, Giffin found only three cases in the literature and added three cases of operation performed in the Mayo Clinic. These cases were characterized by marked splenomegaly, anemia, positive Wassermanns, failure of improvement after antisyphilitic treatment, and treponemes in the walls of splenic vessels. They showed also distinct changes in the liver, and in one, at least, gummas were present. The results in these few cases seem to justify the conclusion that under certain circumstances syphilitic splenomegaly may persist to the point of causing a severe secondary

anemia, and if a thorough trial of antisyphilitic measures is ineffective, splenectomy should be considered.

Chronic Malarial Splenomegaly

The surgery of the chronic malarial spleen apparently has very limited indications, chiefly because, as Osler pointed out, the spleen gradually becomes smaller, although it may take months or even years. There are very few published results of splenectomy for chronic malarial splenomegaly, although Finkelstein advocates splenectomy unless the hemoglobin is below 30 or 40 per cent and there are less than 2,000,000 red blood-corpuscles. Jonnesco and other surgeons have removed the spleen a number of times in such cases, with gratifying results.

Splenic Anemia

The name splenic anemia is applied to a group of cases in which splenomegaly and a leukopenic anemia are the predominating features. Splenic anemia is considered by many, and probably is, a forerunner of Banti's disease, although there seems to be no doubt that it may never progress to the stage described by Banti. As an argument that the two diseases are quite distinct this loses its force when the extreme chronicity of the disease is realized. Typical examples of early splenic anemia and of Banti's disease undoubtedly show marked difference, for Banti's disease is featured by many of the symptoms of an atrophic cirrhosis; in fact, Krull denies Banti's disease as an entity and says it is a form of Laennec's atrophic cirrhosis, and that the liver, not the spleen, is responsible for the condition. Recognizing this difference of opinion, the weight of evidence supports the theory that splenic anemia and Banti's disease are stages of the same disease, and the subject will be reviewed on that basis.

Osler[90] describes the disease as "an intoxication of unknown nature characterized by great chronicity, primary progressive enlargement of the spleen, which cannot be correlated with any known cause (primary splenomegaly), anemia of a secondary type, with leukopenia, a marked tendency to hemorrhage, particularly from the stomach, and in many cases a terminal stage with cirrhosis of the liver and jaundice."

The earliest description of the disease was published in 1866 by Gretsel. In 1871 Wood added materially to the subject. To Banti,[9] in 1894, however, must be given the credit for the first classic description of the later stages of the disease.

The frequency of the disease is difficult to determine. Many cases, especially in the early stages, are undiagnosed or masquerading as other diseases. Many reports of individual cases are found in the literature, and especially since the successful surgical treatment has been recognized, the frequency of the disease has been apparent. In the Mayo Clinic 42 patients have been operated on up to May, 1917, and quite frequently cases are seen (particularly in children and in the late stages of the disease) which, although quite possibly belonging to the splenic anemia group, cannot be positively classified as such.

The etiology of the disease is not established. Many efforts to isolate a microörganism have been made. Gibson states that the parasitic invasion of the spleen can be shown by special staining methods and that the organism is a streptothrix which cannot be isolated in conditions other than splenic anemia. D'Espine and others have been unable to confirm this finding. Gibson believes that three facts point to an infective agent: (1) Extirpation of the spleen cures or alleviates; (2) the disease is similar to kala-azar; and (3) beneficial effects are obtained from salvarsan. Rolleston[108] draws attention to the fact that the cases forming the basis of Gibson's investigation were not typical splenic anemias, but were complicated by various conditions which could well have been primary; for example, tuberculosis, syphilis, and cardiac failure. Hollins believes Bacillus coli the only cause. He considers that the anemia is a hemolytic type, and although no broken-down cells are found in the spleen, he believes that the Bacillus coli is responsible for the hemolysis. He has shown that Bacillus coli has a hemolytic action on blood-cells, and lists several of the diseases which may be produced by it. As corroborative evidence he quotes Adami to the effect that Bacillus coli is occasionally the cause of hepatic cirrhosis. Warthin, believing that splenic anemia and Banti's disease are not entities, states that in all the cases he examined he found a thrombophlebitis of the portal and splenic veins, and concludes that this is the primary condition. This theory has not been largely supported by others, although an apparently identical syndrome can be brought about by portal or splenic thrombosis (Edens, Goldmann, Krumbhaar[77]). Ledingham speaks of a traumatic factor. Banti's own views were that the spleen was responsible because he always found splenic enlargement preceding the anemia, because he noted certain changes in the spleen itself, and because of the therapeutic effects of splenectomy. Hollins in the main believes that the spleen is responsible. He concludes:

(1) That it produces the anemia by increase of its function of hemolysis (Barr), brought about in turn by vasomotor paresis of the splanchnic area (Sutherland and Burghard believe this increased hemolysis is due to loss of vasomotor control of the splenic artery); (2) that the spleen is the center of a chronic infective process; and (3) that the spleen acts mechanically in the production of anemia (Rolleston[106]). Sérégé points out that inasmuch as the larger part of the splenic blood is delivered to the left lobe of the liver, cirrhosis in splenic anemia should be confined to this lobe, but it is not. It is significant that in the majority of cases of cirrhosis the spleen is enlarged, and this fact lends strength to the argument that both organs are attacked simultaneously by the same organism. Hollins produced splenomegaly and anemia in the rabbit by inoculations of Bacillus coli. Yates, Bunting, and Kristjanson have described a diphtheroid organism in the spleens of splenic anemia. Wilson, in repeated examinations of spleens removed from 35 patients with typical splenic anemia, has not observed any organism.

The spleen shows a very marked fibrosis, with atrophy of pulp and Malpighian bodies, and the picture is characteristic enough to distinguish it from the spleen in pernicious anemia, Gaucher's disease, and splenomedullary leukemia. The fact that endarteritis and even patches of calcification sometimes occur in the splenic vein branches explains the friability of these vessels often noted in the operation of splenectomy and the serious operative hemorrhages which occasionally occur. Varicose veins are frequently found at the cardia, and compensatory enlargement of the hemolymph glands has been noted, particularly by Dock and Warthin.

The spleen may be very large, its weight varying from 425 gm. to 5280 gm. (Giffin[52]).

The symptomatology of the disease has been fully described by various observers. The splenomegaly, leukopenic anemia, and tendency to gastric hemorrhage and cirrhosis of the liver are characteristic of the disease. In the early stage the diagnosis will not be confused if the symptoms are pronounced. The blood-picture differentiates pernicious anemia and splenomedullary leukemia. Syphilitic splenomegaly is recognized by the Wassermann and history, and hemolytic jaundice by the acholuric icterus, the crises, an increased red-cell fragility, and evidences of marked hemolysis. Thrombophlebitis of the portal and splenic veins is associated with the same symptoms and signs as splenic

anemia, but is supposed to be accompanied by considerable epigastric pain.

As the later stages of the disease become advanced, diagnosis becomes increasingly difficult and, as has been often pointed out, is at times impossible. The patient who, when first seen, exhibits a large spleen, small liver, ascites, gastro-intestinal and other hemorrhages, and emaciation may be suffering from a primary hepatic cirrhosis or from Banti's disease. The anemia may not be distinctive enough to warrant a diagnosis of the latter. Moreover, even at operation or postmortem a positive diagnosis cannot always be made at such a stage.

Giffin,[25] in reviewing the symptomatology of splenic anemia in the precirrhotic stage in a series of 18 cases in the Mayo Clinic, showed that in this series there were twice as many females as males and that the average age was thirty-seven years. In other series of cases, however, males have been in the majority, Osler[97] reporting 13 in 15 cases. In every case the splenomegaly preceded the anemia. In one case an enlarged spleen had been present twenty years. The blood showed secondary anemia with a leukopenia, in one instance of 1000 leukocytes. In one case only were the leukocytes above normal, that is, 11,000. Hematemesis is considered a frequent manifestation, but had occurred in only 5 of the 18 cases; in Osler's it occurred in 8 out of 15. A history of pain was obtained in 12 cases, in some of which it was of a more or less acute character. Fever is not an infrequent sign in the later stages, but it occurred in only 2 of the early group of 18 cases. Diarrhea was present in 4 cases. The surgical records show that cirrhosis was definite in 5 of the 18 cases. Jaundice was noted twice, in one case without cirrhosis. Recognizable gallbladder disease was present in 18.5 per cent of the cases.

Krumbhaar[77] discusses Banti's division of the symptomatology into three stages: (1) The preascitic stage, which lasts several years. Gradually increasing weakness and pallor are noticed with digestive disturbances and abdominal pain, which may first draw attention to the large spleen. There is an increase of urobilin and a slight leukopenia. (2) The second stage, which lasts but a few months and is characterized by scanty, high-colored urine containing an excess of urobilin, and attacks of dyspepsia and diarrhea with slight increase in the size of the liver. (3) The third stage, that of hepatic cirrhosis with recurrent ascites. As Osler has pointed out, it is important to remember in such cases that ascites may occur without cirrhosis. There is occasionally slight jaun-

17—25

dice and an atrophic liver, with increasing emaciation. Krumbhaar also draws attention to the fact that these stages are frequently not clearly defined.

The treatment indicated is recognized by all writers as being clearly splenectomy. In the early stages the risk is not great and the prospect of permanent cure is excellent. The operative mortality up to 1916 in the Mayo Clinic in 31 cases was 9.6 per cent (Balfour[6]). This includes all cases and every stage of the disease. The mortality, therefore, should be under 10 per cent. This figure can be attained if proper appreciation of the indications for the operation is held.

The late results of operation in the early stage are excellent. Giffin[52] reported that 75 per cent of patients operated on during this stage are in good health. The indication for splenectomy in this stage, therefore, is quite obvious.

In the later stages of the disease, the operative mortality is higher, and when ascites, jaundice, and severe hemorrhages mark the development of an advanced cirrhosis, the operative risk is at least 25 per cent, becoming prohibitive in the terminal stages. Nevertheless, in view of the facts that a fatal outcome is certain in the ordinary course of events, and that removal of the spleen, even in fairly advanced cirrhosis, is followed by apparent cure, or at least arrest of the process, splenectomy should have serious consideration.

THE SPLENIC ANEMIA OF CHILDREN

Anemia with splenomegaly in children has been the subject of much discussion. Hunter divides such anemias into three groups: (1) Those conforming to the adult type; (2) those with a blood-picture showing an increase in leukocytes (between 10,000 and 20,000) and in which normoblasts and megalocytes are found; and (3) those with a high leukocyte count, many normoblasts. Most writers consider Hunter's third group an exaggerated form of the second group.

The large spleen and the type of the anemia would suggest the condition, while a leukopenia, particularly when associated with gastric hemorrhages, would warrant a more or less definite diagnosis. Giffin[54] collected five cases from the literature and reports in detail the case of one patient from the Mayo Clinic, aged thirty months. Haggard has recently reported another case.

Only four cases of splenectomy for the anemia of von Jaksch have been collected from the literature, the most recent one being by Pool.

HEMOLYTIC JAUNDICE

Hemolytic jaundice is a disease characterized by splenomegaly, "non-obstructive" icterus, and anemia. Congenital, familial, and acquired forms are recognized, but it has been the custom in this country to look upon these types as variations of the same disease. Krumbhaar,[77] however, draws attention to the fact that on the continent the congenital and acquired forms are considered as independent conditions, and presents the evidence on which this opinion is based. There are certainly differences, particularly between the familial and acquired types, which may be shown by diagnostic methods and which may be observed clinically. These variations in type are of the greatest interest, and although they have resulted in a temporary confusion, they have produced a wealth of exact information which will be essential in their correlation. It will be safe to assume at the present time and for our present purpose that these many types are variations in degree of the same disease, and they will be so considered here.

Murchison in 1885 drew attention to the occurrence of chronic jaundice in several members of a family, but Hayem is credited with the first description of the disease as a clinical entity. Chauffard made the most important contribution to the subject from the standpoint of diagnosis, in showing the increased fragility of the red blood-cells in the disease. Thayer in 1911 gave the earliest description in this country of the symptomatology of hemolytic jaundice.

Literature dealing with hemolytic jaundice as a surgical entity, especially English literature, is relatively scarce; in fact, Elliott and Kanavel as recently as 1915 presented the first report of splenectomy in this disease that appeared in American literature. They thoroughly reviewed the subject from a surgical standpoint with particular reference to the familial type of several patients they had observed. Giffin[56] in 1917 reviewed twelve cases, including congenital, acquired, and familial types of the disease, in patients operated on in the Mayo Clinic. Peck in 1916 gave a most interesting account of the first patient with the congenital type of the disease operated on in this country (1912). Elliott and Kanavel point out that there were several instances of successful splenectomy prior to the date of the establishment of the clinical entity of the disease (Wells,[123] 1888, Bland-Sutton, 1895).

The relative frequency of the various types is indicated by Krumbhaar[77] in a review of 158 cases, of which 51 per cent were familial (43

per cent of these developing after birth), 14 per cent congenital, and 35 per cent acquired. These percentages probably represent the frequency of each type better than the statistics of a surgical clinic, for a considerable percentage of patients in the familial group are symptomless throughout life as far as general health is concerned, whereas those with the congenital and acquired types have symptoms usually sufficiently severe to lead them to seek relief. Of the 17 patients observed in the Mayo Clinic, "3 were definitely familial, while 6 gave very suggestive histories of familial jaundice" (Giffin[56]).

As yet there has not been a successful effort to place the etiology of the disease on more than a speculative basis, in spite of the fact that the results of splenectomy prove that the spleen is largely concerned in the abnormal hemolysis which is the outstanding feature of the disease.

Krumbhaar[77] gives the two chief views: (1) That there is a primary lesion in the blood, a dystrophy of the red cells; and (2) that either primarily or indirectly in the spleen there is an exaggerated hemolytic activity. As Krumbhaar points out, the writers who hold the former belief (Widal and others) lose sight of the fact that splenectomy is a specific in the disease. Those who hold the spleen responsible (Minkowski, Eppinger,[41] Banti[10]) believe the spleen actively destroys increased numbers of cells and prepares others for destruction. The fact that splenectomy is followed by return of health in these cases and that the clinical evidence of an increased hemolysis disappears, lends the strongest support to the latter view.

The symptomatology of hemolytic jaundice is definite, and the cardinal symptoms are seen in greater or lesser degree in the congenital, familial, and acquired forms. The jaundice is chronic and usually of mild degree, and is an acholuric jaundice with absence of the itching, petechias, clay stool, and brachycardia which are associated with jaundice due to mechanical obstruction of the common bile-duct. Splenomegaly is constant and may be extreme and the liver is usually enlarged. Anemia is not constant, but is common and may be marked, Krumbhaar[77] collecting 10 cases in which there were less than 1,000,000 red blood-corpuscles. The anemia may simulate pernicious anemia (von Stejskal), and Chauffard considers that "there is an icteric form of pernicious anemia which, when accompanied by diminished resistance and reticulated red cells, represents the least compensated form of hemolytic icterus." Epigastric pain is not uncommon and may be severe, simulating gallstone colic, and in many cases is due to gall-

stones. Cholecystitis is probably present in a large percentage of cases, and gallstones have been found in 58 per cent (Giffin[56]).

Exacerbation of these symptoms, together with malaise, headache, enlarged and tender spleen, and occasionally fever, are characteristic of the disease, especially in the acquired form.

In special diagnostic tests, the fragility of the red blood-corpuscles is of most importance. It is consistently increased in this disease. The urine does not contain bile-salts except under exceptional circumstances (during a crisis), but bile-pigment is always found in the blood, and urobilin in the urine. An approximation of the degree of hemolysis may be made by the method of Schneider of extracting the duodenal contents by means of a tube, and estimating the quantities of urobilin and urobilinogen. Widal, Abrami, and Brulé find the auto-agglutination test positive in the acquired form, and always negative in the congenital or familial form.

The diagnosis of hemolytic jaundice, therefore, is usually not difficult, and is confusing only in the atypical cases. The close relationship of the disease to Hanot's cirrhosis, symptomatically at least, is to be remembered (Mayo[89]).

Surgical treatment of the disease is clearly indicated if the symptoms are at all pronounced or the crises disabling. Difference of opinion exists as to the treatment of hemolytic icterus associated with indefinite and infrequent and mild crises. Undoubtedly many such patients live a normal length of life without inconvenience, and operation may be justifiably postponed until subjective symptoms become more marked. The indication for operation, therefore, is dependent largely on the severity of the disease, the frequency of crises, the symptomatic evidence of developing complications, and the degree of anemia present. When the blood-picture indicates marked hemolysis, operation should be seriously considered.

The results of splenectomy in the disease are excellent, and the collected cases show a lower operative mortality than in any other condition for which splenectomy has been advocated. Elliott and Kanavel in 1915 tabulated 48 cases in which there were 2 deaths. The patients recovering from the operation obtained a symptomatic cure and sufficient time has elapsed in some of the cases to warrant the belief that the change is permanent. Curiously, although there was an immediate improvement in the blood-picture of all the patients, the increased

fragility of the red blood-corpuscles, which was a constant feature previous to operation, did not consistently return to normal (Giffin).

Since the adoption of Schneider's method of estimating the urobilin and urobilinogen in the duodenal contents, interesting observations have been possible. Giffin[56] has shown, in a study of the patients operated on in the Mayo Clinic, that the quantity of bile-pigments, which is always increased in the disease, just as constantly tends to approximate the normal following splenectomy. Splenectomy gives its most impressive result in hemolytic jaundice.

Cirrhosis of the Liver

In the past few years considerable attention has been directed to the problem of the rôle of the spleen in cirrhosis of the liver. Many observers, particularly Rolleston,[107] have attributed certain types of hepatic cirrhosis to poisons originating in the spleen. Reference has already been made to the intimate association between spleen and liver in splenic anemia, and to the fact that splenectomy, even when cirrhosis and ascites had developed, has produced most distinct benefit. This fact, together with much clinical and experimental evidence, gives the spleen a prominent place as an etiologic factor in the group of infectious cirrhoses. The determination of the indication for, and the true value of, splenectomy under such circumstances is not easy because of the inherent difficulties in both clinical and surgical diagnosis. The strong similarity between the hypertrophic cirrhosis of Hanot and hemolytic jaundice (as pointed out by Mayo[89]), and the difficulty in differentiating certain types of cirrhosis, both in the hypertrophic and atrophic stages, from splenic anemia, even at operation, are well-known examples proving the necessity of very careful investigation of this subject.

Eppinger and Ranzi and others have strongly advocated splenectomy in all cases of hypertrophic cirrhosis of the liver when the spleen is large and there is extreme jaundice, especially in the absence of a history of alcoholism. Rolleston[107] also states that "in cirrhosis due to poisons manufactured in the spleen, splenectomy is a logical, if heroic, form of treatment."

In this country there are few records of splenectomy in cases which were considered primary hepatic cirrhosis. Four cases have been reported from the Mayo Clinic, the immediate results of which have been promising.

GASTRO-INTESTINAL HEMORRHAGE

To what extent a small or slightly enlarged spleen can be held responsible for some of the cases of otherwise unexplained gastric and gastro-intestinal hemorrhages is not known, but there is already sufficient evidence to make it most important to consider the spleen in these cases of obscure gastric hemorrhage. Such evidence is furnished by the facts that in certain diseases in which gastro-intestinal hemorrhages are common, splenectomy is curative; that gastric hemorrhage may be caused by a distant toxic focus (appendix, gallbladder, etc.); that the spleen may similarly act as a focus of infection and bring about gastric hemorrhage either primarily or through the medium of the liver.

In discussing the rôle of the spleen under such circumstances I[8] reported the case of a patient from whom I removed a slightly enlarged spleen on the assumption that it was the cause of repeated gastric hemorrhages which had subjected the patient to various operations, particularly gastric, but had continued to the point of almost costing his life. Hemorrhage ceased following the splenectomy, and the patient has been in excellent health since. Under such circumstances splenectomy could be justified only after the positive exclusion of every other causative lesion or focus of infection.

THROMBOPHLEBITIS OF SPLENIC AND PORTAL VEINS

Varying degrees of thrombosis of the splenic vein have been described in connection with splenomegaly, and especially in splenic anemia. This finding has suggested that the condition is an etiologic factor in certain cases of splenomegaly, and that thrombophlebitis of the splenic and portal veins occurs as a primary condition, that it is a clinical entity and is associated with a rather definite clinical picture in which enlargement of both spleen and liver, ascites, epigastric pain, and possibly a history of traumatism are features. Rolleston[107] suggested splenectomy in such a condition, and Tansani and Morone report a case of splenectomy in the third stage of Banti's disease in which the splenic vein and its branches were changed into hard cords. They admit, however, the uncertainty as to the primary condition, although Banti thought it was not a primary splenomegaly.

GAUCHER'S DISEASE

Originally considered by Gaucher (1882) as a true neoplasm, this disease is now looked on as clinically non-malignant. Brill and Mandle-

baum showed that the changes found in the spleen were not confined to that organ, but that similar endothelial proliferation could be demonstrated both in lymph-nodes and bone-marrow. They also described certain clinical features of the disease. The onset occurs usually in childhood, with a chronic course (average, twenty years), although Niemann reports an apparently acute form of the disease. In many respects, particularly in the character of the anemia (of a moderate degree and with a leukopenia) and in the tendency to mucosal hemorrhages, Banti's disease is simulated. The splenic enlargement is supposed to be greater than in other diseases associated with splenomegaly. Krumbhaar[77] states that the disease has been recognized before operation on four occasions, once by splenic puncture. It cannot be expected, inasmuch as there is disagreement among pathologists as to the authenticity of some of the cases reported as Gaucher's disease, that the late operative results will be as yet accepted. Krumbhaar, for example, states that a "cure can hardly be expected, as the disease is known to exist independently in bone-marrow and lymph-nodes." Nevertheless, patients with apparently substantiated Gaucher's disease are living several years after operation in good health, with every indication of a permanent cure.

PERNICIOUS ANEMIA

The actual and relative value of splenectomy in pernicious anemia is as yet to be proved. The group of patients who have been splenectomized in this country for pernicious anemia during the last three years is sufficiently large to permit conclusions as to the results of the operation, but any conclusions as to final results will be acceptable only when a considerable period of time has elapsed since the operation. It is most important, however, to remember that an investigation of the condition of these patients at the present time is quite useless as a criterion of the effect of splenectomy on the disease itself.

From the available operative results, certain facts may be recorded. For instance, Krumbhaar[79] has shown that during the earlier experience with the operation the deaths occurring immediately or within six weeks after splenectomy reached as high as 20 per cent. It soon became apparent that many of these deaths were due not to the inherent risks of the operation, but to the condition of the patient. As soon, therefore, as the unwarranted surgical risks were avoided the operative mortality dropped well below 5 per cent. The more intelligent selection of cases

for splenectomy was the result of the recognition of the fact that the operation itself was of high risk in certain stages of the disease, and that even if the patient recovered, a remission of symptoms could not be reasonably expected.

That splenectomy will effect a more prompt and more prolonged remission of symptoms than has been possible under previous methods is the opinion of the majority of those who have been in a position to observe large series of cases (Cabot, Moffitt, Krumbhaar,[79] Giffin,[57] Percy, and others). But there is as yet no proof that splenectomy will cure the disease, or even bring about a permanent arrest of symptoms. Despite encouraging earlier reports it is found, as time goes on, that in many of the promising cases there are recurrences, or that in some instances the patients have died, so that the value of splenectomy becomes increasingly dubious. Percy, however, is quite sanguine over the results he has obtained by removing other possible foci of infection, particularly the gallbladder and appendix, at the same time that he performed the splenectomy.

The present status of splenectomy in pernicious anemia as indicated in the reports from various sources, therefore, is as follows: (1) The operation has no place in advanced stages of the disease; (2) under certain conditions the operation may be justifiably advised, that is, when a patient not beyond middle life gives only a short history of the condition, the anemia is moderate in degree, the spleen is enlarged, the skin is icteroid, there is a definitely high hemolysis, and nothing more than a temporary remission can be promised, and (3) transfusions of blood both before and after splenectomy are a most useful adjunct to the operation.

SPLENOMEDULLARY LEUKEMIA

The results of the surgical treatment of splenomedullary leukemia in the past have been very discouraging. The earlier operative experience was associated with such a high initial mortality that the operation was practically abandoned.

Warren, who in 1911 reported one case of splenectomy for this condition followed by recovery, and referred to the 42 cases collected by Hagen with 4 recoveries, attributed the serious operative risk to secondary hemorrhage from the wound. It must be remembered that at the time these unfavorable results were reported splenectomy was performed during the active period of the disease, and when the number of white cells was large, showing a high ratio to the red cells. There have been

since that time isolated reports of splenectomy for splenomedullary leukemia, in some of which the diagnosis was rather seriously doubted (Richardson).

The surgical profession has hesitated, therefore, to adopt operative measures in this disease, but since it has been demonstrated that radium, x-rays, and benzol exert a specific, although temporary, effect on the symptoms of myelogenous leukemia (Billings and others), splenectomy has again come up for consideration. Radium appears to exert the most powerful influence on the spleen and on the blood-picture, and there have been several cases reported of remissions that have been produced by radium in conditions entirely resistant to x-rays and benzol (Ordway, Giffin[58]).

The therapeutic value of these agents being sufficient to bring the blood-picture to normal, to greatly improve the patient's general condition, and to gradually reduce the size of the spleen (in some instances until it is non-palpable), suggested the possibility that removal of the spleen at this stage might have some influence on the course of the disease, particularly if these therapeutic agents were used as adjuncts. It has already been demonstrated that under such circumstances splenectomy may be done with a very low operative mortality. In the Mayo Clinic since October 2, 1916, 17 patients have been operated on with splenomedullary leukemia in which the blood-picture had been first brought to normal by the use of radium, x-rays, or benzol, or a combination of these agents. There have been no operative deaths in this series, but we have as yet no knowledge as to the ultimate results of the operation.

Unclassified Splenomegaly

There are finally a number of cases of splenomegaly which cannot as yet be classified. This group will include: (1) Simple or idiopathic splenomegaly, which may persist for years without any anemia; (2) splenomegaly with eosinophilia, one instance of which is reported by Giffin;[53] (3) chronic polycythemia with splenomegaly, a group described by Osler;[98] (4) chronic septic splenomegaly, in which moderate enlargement of the spleen occurs with anemia, a condition thought to be due to preceding abdominal or systemic sepsis; (5) Egyptian splenomegaly, in which there is an acute course, with high fever and rapid development of large spleen and liver, without evidence of sepsis and without jaundice (one similar case has been reported by Giffin[53]); and (6) the tropical splenomegalies, kala-azar, etc., which, to my knowledge, have

not been classified and in which, as yet, surgical treatment has not had an extensive trial.

In conclusion it should be emphasized that in diseases of the spleen it is absolutely essential that the surgeon should realize that physical findings are of minor importance, and that a correct diagnosis must depend on the clinician, who in turn must in large part rely on the various laboratory findings and special diagnostic methods. In such instances, therefore, the surgeon takes his cue from the clinician and then adds his opinion as to the advisability of splenectomy, an opinion which will be based on the condition of the patient and the probable benefits that will be gained from the operation.

TECHNIC OF SPLENECTOMY

The surgery of the spleen is practically confined to splenectomy, although ligation of the blood-supply may have limited usefulness. The incision usually preferred is in the left rectus. The length of the incision varies with the size of the spleen, is continued upward to within an inch of the costal margin, and in the presence of a very large spleen parallels the costal margin to the midline if necessary. Some surgeons (Warren) use a "T" incision when a large spleen is to be removed. Others speak of the occasional advisability of rib resection (Meyer). Kanavel[39] recommends elevation, tilting the body by means of sand-bags, in order to facilitate the operation. The necessity for the best possible exposure is indicated by these various suggestions.

The importance of a careful abdominal exploration is emphasized by Kanavel and others, in view of the frequent gallbladder and liver complications in the diseases for which splenectomy is advocated. The essential features in the operation as performed at present in the Mayo Clinic and which I[7] have previously described are as follows:

1. The accessory adhesions and gastrosplenic omentum are separated, divided, and ligated. Division of the gastrosplenic omentum frees the fundus of the stomach, which comes into view in every instance and must be carefully protected from injury.

2. The dislocation of the spleen may be accomplished in the majority of instances by stripping the adhesions with the fingers. In a few cases it is necessary to divide adhesions between clamps. After the spleen has been displaced from its diaphragmatic and renal position, a large pack may be introduced into the space formerly occupied by the spleen. This pack serves to support the spleen, and if it is well placed and left

undisturbed until all other steps in the operation are completed, will often obviate the ligation of veins of some size which might entail much technical difficulty.

3. The spleen is now carefully elevated and tracted toward the midline, and unless accessory vessels are encountered along the posterior border of the pancreas, the pedicle may be ligated. The pancreas occasionally comes into the operative field, usually over the posterior aspect of the pedicle, and in some instances the tail of the organ must be displaced before the pedicle can be ligated. A very exact and safe method is first carefully to expose and individualize the arterial and venous branches in the pedicle from the posterior aspect by dividing the fibrous investment of the pedicle. The successive division of each arterial and venous trunk, beginning with the lateral vein on each side of the fan-shaped pedicle, will permit a very useful mobilization of the spleen, so that the clamping of the central portion of the pedicle, which usually contains the splenic artery or its largest branch, is very much favored. It is rare that such a method is not feasible, and in such event ligation *en masse*, preferably by the two-clamp method, can be carried out. Gerster in 1915 suggested the preliminary ligation of the arterial supply in order to conserve as much as possible of the blood in the spleen by forcing it out through unclamped veins by manual compression of the spleen. Lockwood recently suggested the use of the method of Lichtenstein, that is, the reintroduction of the blood, which can be expressed from the removed spleen into the patient's veins.

Under favorable circumstances splenectomy is not a difficult or dangerous operation. Many surgeons, however, have referred to the unexpected and serious difficulties which may be encountered through hemorrhage, either from the pedicle itself or from accessory veins. A methodical operation will minimize such possibilities, but will not entirely obviate them. Troublesome bleeding is usually venous, and can therefore be temporarily controlled by the pressure of a gauze pack until the spleen is removed. Usually such torn veins can be ligated, but it may be necessary to leave the gauze pack in place until a few days later. When the bleeding can be controlled with forceps, but the vessels cannot be safely ligated because of their friability, the forceps may be left in position. At the end of seventy-two hours they may be loosened and, if no oozing has taken place, removed in eight or ten hours.

It is therefore of great importance to anticipate such operative complications. This can be accomplished in large measure by the routine of first dividing and ligating the gastrosplenic omentum and all

accessory adhesions possible before attempting the mobilization of the spleen.

The danger of injuring the stomach or pancreas has already been referred to and was early emphasized by Mayo.[88]

The difficulties in the operation of splenectomy are to some extent dependent on the disease or condition for which the operation is performed. In pernicious anemia, for example, splenectomy is practically never attended by technical difficulty. In hemolytic jaundice the operation is usually without special risk, although the spleen is occasionally very large. Splenic anemia is most frequently associated with high operative risk, particularly in advanced stages of the disease, oftentimes due, as has already been mentioned, to the thrombotic changes in the splenic and accessory veins. The same is true in hepatic cirrhosis. In diseases which occur with less frequency splenectomy has no special risks.

The postoperative course of splenectomized patients depends also to a large extent on their condition at operation. For example, in the cirrhotic and ascitic stages of splenic anemia, convalescence is protracted and uncertain. If a patient is a good surgical risk and the operation not of extraordinary difficulty, the postoperative course compares favorably with that of any other major abdominal operation.

Of the actual complications it would be expected, and it is true, that left-sided pleurisy, with or without fluid, would occur with greater frequency than in other abdominal operations.

The occurrence of a rise in temperature on the second or third day in some cases has been the subject of some speculation. Bland-Sutton has attributed it to infection in the stump of the pedicle, others to pancreatic disturbance.

BIBLIOGRAPHY

1. Adami, J. G.: The principles of pathology. Phila., Lea, 1908, p. 426.
2. Adami, J. G., and Nicholls, A. G.: Principles of pathology. Phila., Lea, 1909, ii, 222.
3. Alexander, R. C., and Romanes, A.: Accessory spleen causing acute attacks of abdominal pain. Lancet, 1914, ii, 1089–1091.
4. Andral, G.: Précis d'anatomie pathologique. Paris, Gabon, 1829, ii, 431. Quoted by Heinricus, G.: Ueber die Cysten der Milz und über ihre Behandlung speciell durch Splenectomie. Arch. f. klin. Chir., 1904, lxxii, 138–171.
5. Balfour, D. C.: Non-strangulated diaphragmatic hernia due to indirect injury. Ann. Surg., 1916, lxiii, 78–82.
6. Balfour, D. C.: The spleen in its relationship to pernicious anæmia, splenic anæmia and hæmolytic jaundice. Canad. Jour. Med. and Surg., 1916, xl, 47–57.
7. Balfour, D. C.: The technic of splenectomy. Surg., Gynec. and Obst., 1916, xxiii, 1–6.
8. Balfour, D. C.: Splenectomy for repeated gastro-intestinal hemorrhages. Ann. Surg., 1917, lxv, 89–94.
9. Banti, G.: La splenomegalia con cirrosi epatica. Sperimentale, 1894, sez. biol., xlviii, 407. Quoted by Krumbhaar, loc. cit., 77.

10. Banti, G.: La splénomegalie hémolytique. Semaine méd., 1912, xxxii, 265; Abst. Jour. Amer. Med. Assn., 1912, lix, 73.
11. Barr, J.: Three cases of Banti's disease. Lancet, 1902, ii, 493–497.
12. Berger: Quoted by Willis, loc. cit.
13. Billings, F.: Benzol in the treatment of leukæmia. Jour. Am. Med. Assn., 1913, lx, 495–498.
14. Bircher, E.: Ein Beitrag zur Chirurgie der nicht-parasitären Milzcysten. Deutsch. Ztschr. f. Chir., 1908, xcii, 323–351.
15. Boeckelmann, T. W. A.: Quoted by Fowler, loc. cit.
16. Boettcher: Ueber die Entwicklung von Milzcysten. Dorpater med. Ztschr., 1870, i, 287. Quoted by Heinricus, G.: Ueber die Cysten der Milz und über ihre Behandlung speciell f. klin. Chir., 1904, lxxii, 138–171.
17. Brill, N. E., and Mandlebaum, F. S.: Large-cell splenomegaly (Gaucher's disease); a clinical and pathological study. Am. Jour. Med. Sc., 1913, cxlvi, 863–883.
18. Bryan, W. A.: Cysts of the spleen. Jour. Am. Med. Assn., 1905, xlv, 680–684.
19. Burke: Dublin Jour. Med. Sc., 1889, xlvii, 540. Quoted by Douglas and Eisenbrey, loc. cit.
20. Bush, C.: Primary sarcoma of the spleen. Jour. Am. Med. Assn., 1910, liv, 453–456.
21. Cabot, R. C.: Pernicious anæmia. In Modern Medicine. Osler, W., and McCrae, T. Phila., Lea, 1915, iv, 644.
22. Cannaday, J. E.: Spontaneous rupture of the spleen. Surg., Gynec. and Obst., 1915, xxi, 747–749.
23. Carpenter, G.: Splenomegaly in infants and young children. Brit. Med. Jour., 1903, ii, 463–469.
24. Carstens, J. H.: A short history of splenectomy. N. Y. Med. Jour., 1905, lxxxii, 1051–1053.
25. Chalatow, S. S.: Zur Frage über die metastatische Geschwulstbildung in der Milz. Virchow's Arch. f. path. Anat., 1914, ccxvii, 140–160.
26. Chauffard, A.: Pathogénie de l'ictère congénitale de l'adulte. Semaine méd., 1907, xxvii, 25. Quoted by Krumbhaar, loc. cit., 77.
27. Clarke, T.: Ephemerides natur. curios. Ann. iv, v, 1676. Quoted by Krumbhaar, loc. cit., 78.
28. Coley: Tubercles in the spleen. Tr. Path. Soc., Lond., 1848, i, 276–277.
29. Council, M. D.: Primary sarcoma of the spleen. Ann. Surg., 1912, lvi, 915–924.
30. Coupland, S.: Splenic anæmia; splenomegalie primitive. Brit. Med. Jour., 1896, i, 1445.
31. Deaver, J. B.: Sarcoma of the spleen; splenectomy; recovery. Internat. Clin., 1914, 24s., iii, 208–210.
32. Dege: Ueber Tumoren der Milzgegend. Veröffl. a. d. Geb. d. Milz-San. Wis., Berl., 1906, pt. 35, pp. 487–513. Quoted by Doebbelin, loc. cit.
33. D'Espine, A.: La maladie de Banti chez l'enfant. Arch. f. Kinderh., 1913, lx, 254–266.
34. Dock, G., and Warthin, A. S.: A clinical and pathological study of two cases of splenic anæmia with early and late stages of cirrhosis. Am. Jour. Med. Sc., 1904, cxxvii, 24–55.
35. Doebbelin: Fall von sequestrierendem Milzabszess. Deutsch. med. Wchnschr., 1907, ii, 1326–1328.
36. Douglas, J., and Eisenbrey, A. B.: Tuberculosis of the spleen, septic infarction, polycythæmia, splenectomy. Am. Jour. Med. Sc., 1914, cxlvii, 479–493.
37. Dowd, C. N.: Cavernous angioma of the spleen. Ann. Surg., 1915, lxii, 177–181.
38. Edens: Ueber Milzvenenthrombose, Pfortaderthrombose und Bantische Krankheit. Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1908, xviii, 59–79.
39. Elliott, C. A., and Kanavel, A. B.: Splenectomy for hæmolytic icterus; a discussion of the familial and acquired types, with a report of the splenectomized cases. Surg., Gynec. and Obst., 1915, xxi, 21–37.
40. Elting, A. W.: Abscess of the spleen. Ann. Surg., 1915, lxii, 182–192.
41. Eppinger, H.: Zur Pathologie der Milzfunktion. Berl. klin. Wchnschr., 1913, ii, 1509–1512, 1572–1576, 2409–2411.
42. Eppinger, H., and Ranzi, E.: Ueber Splenektomie bei Bluterkrankungen. Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1914, xxvii, 796–806.
43. Fauntleroy, A. M.: Traumatic rupture of the spleen. Ann. Surg., 1913, lvii, 68–71. Quoted by Willis, loc. cit.
44. Federmann: Ueber einen Fall von operativ geheiltem Milzabscess nach Typhus abdominalis. Deutsch. med. Wchnschr., 1905, i, 586–588.

45. Finkelstein, B. K.: Surgery of the spleen (sixty-six cases). Brit. Jour. Surg., 1914–15, ii, 68–76.
46. Fowler, R. H.: Cysts of the spleen. Ann. Surg., 1913, lvii, 658–690.
47. Franke, F.: Ueber die primäre Tuberculose der Milz. Deutsch. med. Wchnschr., 1906, ii, 1656–1659.
48. French, H., and Turner, P.: Case of splenic anæmia treated by splenectomy. Proc. Roy. Soc. Med., Lond., 1913–14, vii, Clin. Sect., 77–79.
49. Gaucher, P. C. E.: De l'épithélioma primitif de la rate, hypertrophie idiopathique de la rate sans leucemie, Par., 1882, 31 p.
50. Gerster, J. C. A.: Ligation of the splenic and gastro-epiploica sinistra arteries in the surgery of the spleen. Jour. Am. Med. Assn., 1915, lxv, 527.
51. Gibson, A. G.: The infective nature of certain cases of splenomegaly and Banti's disease. Quart. Jour. Med., 1913–14, vii, 153–164.
52. Giffin, H. Z.: Clinical observations concerning twenty-seven cases of splenectomy. Am. Jour. Med. Sc., 1913, cxlv, 781–795.
53. Giffin, H. Z.: Clinical notes on splenectomy. Ann. Surg., 1915, lxii, 166–171.
54. Giffin, H. Z.: Splenectomy for splenic anæmia in childhood and for the splenic anæmia of infancy. Ann. Surg., 1915, lxii, 679–687.
55. Giffin, H. Z.: The treatment by splenectomy of splenomegaly with anæmia associated with syphilis. Am. Jour. Med. Sc., 1916, clii, 5–16.
56. Giffin, H. Z.: Hæmolytic jaundice: a review of seventeen cases. Surg., Gynec. and Obst., 1917, xxv, 152–161.
57. Giffin, H. Z.: A report on the treatment of pernicious anæmia by transfusion and splenectomy. Jour. Am. Med. Assn., 1917, lxviii, 429–432.
58. Giffin, H. Z.: Observations on the treatment of myelocytic leukæmia by radium. Presented before Ass. Am. Physicians, May 2, 1917. Published in Boston Med. and Surg. Jour., 1917, clxxvii, 686–691.
59. Goldmann, G.: Zur Kasuistik der Milzvenen und Pfortaderthrombose. Deutsch. med. Wchnschr., 1913, ii, 1542–1545.
60. Green, C. C.: Stab wounds of the chest involving the diaphragm. Jour. Am. Med. Assn., 1916, lxvii, 178–179.
61. Gretsel: Ein Fall von Anæmia splenica bei einem Kinde. Berl. klin. Wchnschr., 1866, iii, 212–214.
62. Hagen, F. G.: Ein Beitrag zur Milzchirurgie. Arch. f. klin. Chir., 1900, lxii, 188–231. Quoted by Warren, loc. cit.
63. Haggard, W. D.: Splenectomy in the anæmias and other blood states associated with enlargement of spleen and liver. Jour. Am. Med. Assn., 1917, lxix, 79–81.
64. Halpenny, J.: Tuberculosis of the spleen. Canad. Med. Assn. Jour., 1914, iv, 1091–1094.
65. Hamann, H. F. F.: Statistik der Tuberkulose im Alter von 16–90 Jahren. Kiel, Schmidt, 1890. Quoted by Winternitz, loc. cit.
66. Hartwell, J. A.: Splenomegaly with anæmia in a syphilitic patient. Med. Rec., 1914, lxxxv, 593.
67. Hayem, G.: Sur un variété particulière d'ictère infectieux chronique splenomegalique. Presse méd., 1898, i, 121–125. Nouvelle contribution à l'étude de l'ictère infectieux chronique splénomegalique. Bull. et mém. Soc. méd. d. hôp. de Par., 1908, xxv, 122. Quoted by Krumbhaar, loc. cit., 77.
68. Hollins, T. J.: Primary splenomegaly or splenic anæmia: a critical study, with special reference to the pathogenesis. Practitioner, Lond., 1915, xciv, 426–462.
69. Hollister, J. C.: Das Verhalten der Milz bei Carcinom. Deutsch. med. Wchnschr., 1906, ii, 1498–1499.
70. Hunter, W. K.: Infantile splenic anæmia, with notes of ten cases. Lancet, 1909, i, 230–235.
71. Jepson, W., and Albert, F.: Primary sarcoma of the spleen and its treatment by splenectomy. Ann. Surg., 1904, xl, 80–97.
72. Johnson, A. B.: Surgical diagnosis. New York, Appleton, 1909, ii, 185. Quoted by Willis, loc. cit.
73. Jonnesco, T.: Splénectomie pour mégalosplenie malarienne, complications postoperatoires. Bull. et mém. Soc. de chir. de Bucarest, 1899–1900, ii, 3–7.
74. Jonnesco, T.: Splénectomie pour hypertrophie paludéene. Bull. et mém. Soc. de chir. de Par., 1900, ii, 112.
75. Jonnesco, T.: Splenectomy for malarial cachexia. Internat. Clin., 1902, 11 s., iv, 221–231.

76. Krull, J.: Ueber die Bantische Krankheit. Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1915, xxviii, 718–748; Abst. Jour. Am. Med. Assn., 1915, lxv, 750.

77. Krumbhaar, E. B.: A classification and analysis of clinical types of splenomegaly accompanied by anæmia. Am. Jour. Med. Sc., 1915, cl, 227–245.

78. Krumbhaar, E. B.: The history of extirpation of the spleen. N. Y. Med. Jour., 1915, ci, 232–234.

79. Krumbhaar, E. B.: Late results of splenectomy in pernicious anæmia. A statistical and critical review. Jour. Am. Med. Assn., 1916, lxvii, 723–727.

80. Kuettner, H.: Ueber sequestrierende Milzabscesse. Beitr. z. klin. Chir., 1907, liv, 405–457.

81. Langhans, T.: Casuistische Beiträge zur Lehre von den Gefässgeschwulsten. 1. Pulsirende cavernöse Geschwulst der Milz mit metastatischen Knoten in der Leber. Tödtlicher Verlauf binnen 5 Monaten. Virchow's Arch. f. path. Anat., 1879, lxxv, 273–291.

82. Lanz: Ligatur der Arteria-splenica bei fixierter Wandermilz. Zentralbl. f. Chir., 1914, i, 228–231.

83. Ledingham, J. C. G.: Splenic anæmia. A system of medicine: In Albutt, C., and Rolleston, H. D. London, Macmillan, 1909, v, 765.

84. Lichtenstein: Quoted by Lockwood, loc. cit.

85. Lockwood, C. D.: The surgical treatment of Banti's disease. Surg., Gynec. and Obst., 1917, xxv, 188–191.

86. McDonald, I., and Mackay, W. A.: A case of acute torsion of a wandering spleen; splenectomy; recovery. Lancet, 1909, ii, 917.

87. Matthia, N.: Ephemerides med. physicar. natur. curiosor., Decuria ii, Ann. ii (1684), Noremberg, 1685. Observ. cxcv. Quoted by Krumbhaar, loc. cit., 78.

88. Mayo, W. J.: Surgery of the spleen. Surg., Gynec. and Obst., 1913, xvi, 233–239.

89. Mayo, W. J.: Some of the maladies in which splenectomy may be indicated. Lancet, 1916, ii, 889–892.

90. Meyer, W.: Splenectomy for splenic anæmia (resection of costal arch). Ann. Surg., 1909, xlix, 258–260.

91. Minkowski, O.: Ueber einem hereditärischen unter dem Bild eines chronischen Ikterus mit Urobilinurie, Splenomegalie und Nierensiderosis verlaufende Affektion. Verhandl. d. deutsch. Kong. f. innere Med., 1900, xviii, 316. Quoted by Elliott and Kanavel, loc. cit.

92. Moffitt, H. C.: The function of the spleen, with particular reference to hæmolysis and the hæmolytic anæmias. Boston Med. and Surg. Jour., 1914, clxxi, 289–300.

93. Monerret, E.: Étude sur une maladie complexe de la rate. Arch. gen. de méd., 1859, 5 s., xiv, 513–524. Quoted by Winternitz, loc. cit.

94. Murchison, C.: Clinical lectures on diseases of the liver, jaundice and abdominal dropsy. Ed. 3, Lond., Longmans, 1885, p. 481. Quoted by Krumbhaar, loc. cit., 77.

95. Niemann, A.: Ein unbekanntes Krankheitsbild. Jahrb. f. Kinderh., 1914, xxix, 1–10. Quoted by Krumbhaar, loc. cit., 77.

96. Ordway, T.: Remissions in leukæmia produced by radium in cases completely resistant to X-ray and benzol treatment. Tr. Assn. Am. Physicians, 1916, xxxi, 177–207.

97. Osler, W.: On splenic anæmia. Am. Jour. Med. Sc., 1900, cxix, 54–73.

98. Osler, W.: Chronic cyanosis with polycythæmia and enlarged spleen; a new clinical entity. Am. Jour. Med. Sc., 1903, n. s., cxxvi, 187–201.

99. Osler, W.: Splenic anæmia. In Modern Medicine: Osler, W., and McCrae, T. Ed. 2, Phil., Lea, 1915, iv, 954.

100. Peck, C. H.: Splenectomy for hæmolytic jaundice. Jour. Am. Med. Assn., 1916, lxvii, 788–790.

101. Percy, N. M.: Splenectomy. Illinois Med. Jour., 1916, xxx, 118–120.

102. Pool, E. H.: Anæmia in an infant. Ann. Surg., 1915, lxi, 349–351.

103. Powers, C. A.: Non-parasitic cysts of the spleen. Ann. Surg., 1906, xliii, 48–60.

104. Quittenbaum, K. S.: Commentarii de splenis hypertrophiae et historiae extirpationis, etc. Rostock, 1836. Quoted by Krumbhaar, loc. cit., 78.

105. Rendu and Widal: Splénomégalie tuberculeuse sans leucemie avec, hyperglobulie et cyanose. Bull. et mém. Soc. méd. d. hôp. de Par., 1899, 3 s., xvi, 528–541. Quoted by Douglas and Eisenbrey, loc. cit.

106. Richardson, M. H.: Splenectomy for myelogenous leukæmia. Ann. Surg., 1905, xlii, 656–660.

107. Rolleston, H. D.: Diseases of the liver, gall-bladder, and bile-ducts. Lond., Macmillan, 1912, pp. 188, 299.
108. Rolleston, H. D.: Chronic splenic anæmia and Banti's disease. Practitioner, Lond., 1914, xcii, 470–486.
109. Schneider, J. P.: The splenic pathology of pernicious anæmia and allied conditions. Arch. Int. Med., 1916, xvii, 32–41.
110. Senator, H., and Litten, M.: Disease of the kidney and of the spleen. In Nothnagel's Encyclopedia of Practical Medicine, Phil., Saunders, 1905, pp. 662–663. Quoted by Cannaday, loc. cit.
111. Sérégé, H.: Étude sur l'indépendance anatomique et physiologique des lobes du foie. J. de méd. de Bordeaux, 1902, xxxii, 327–329. Quoted by Hollins, loc. cit.
112. Sherren, J.: A case of hydatid cyst of the spleen. Brit. Jour. Surg., 1914–15, ii, 341–343.
113. Smith, M. A.: Splenectomy for carcinoma. Ann. Surg., 1908, xlvii, 53–56.
114. Stejskal, K. R., von: Ueber haemolytischen Ikterus und über das Auftreten haemolytischer Vorgänge bei diesem und bei perniciöser Anämie. Wien. klin. Wchnschr., 1909, xxii, 661–667.
115. Still, G. F.: Gumma of the spleen in children. Tr. Path. Soc. Lond., 1897, xlviii, 205–209.
116. Sutherland, G. A., and Burghard, F. F.: Treatment of splenic anæmia by splenectomy. Proc. Roy. Soc. Med., 1910–11, iv, Clin. Sect., 58–70.
117. Sutton, J. B.: Observations on the surgery of the spleen. Brit. Jour. Surg., 1913–14, i, 157–172.
118. Tansani, I., and Morone, G.: Splénomégalie avec cirrhose hépatique en période ascitique; splénectomie et opération de Talma; contribution à l'étude et au traitement des splénomegalies chroniques splénothrombosiques. Rev. de chir., 1913, xlviii, 263–312. Quoted by Rolleston, loc. cit.
119. Thayer, W. S.: Hæmolytic jaundice. Illinois Med. Jour., 1911, xix, 174.
120. Theile: Ueber Angiome und sarkomatöse Angiome der Milz. Virchow's Arch. f. path. Anat., 1904, clxxviii, 296–323.
121. Thomas, J. D.: Hydatid disease, with special reference to its prevalence in Australia. Adelaide, 1884. Quoted by Fowler, loc. cit., and Sherren, loc. cit.
122. Troell, A.: On ligation of splenic vessels as a substitute for splenectomy in blood diseases. Ann. Surg., 1916, lxiii, 88–105.
123. Wallace, C.: A study of 1,200 cases of gunshot wounds of the abdomen. Brit. Jour. Surg., 1917, iv, 679–743.
124. Warren, J. C.: The surgery of the spleen. Ann. Surg., 1901, xxxiii, 513–543.
125. Warthin, A. S.: The relation of thrombophlebitis of the portal and splenic veins to splenic anemia and Banti's disease. Internat. Clin., 1910, 20 s., iv, 189–221.
126. Webb, C. H. S., and Milligan, E. T. C.: Notes on thirty-two cases of penetrating wounds of the abdomen. Brit. Jour. Surg., 1916, iv, 338–367.
127. Wells, T. S.: On excision of an enlarged spleen. Med. Times and Gaz., 1866, i, 2. Quoted by Krumbhaar, loc. cit., 78.
128. Wells, T. S.: Remarks on splenectomy, with a report of a successful case. Med.-Chir. Tr., 1888, lxxi. Quoted by Elliott and Kanavel, loc. cit.
129. Widal, F., Abrami, P., and Brulé, M.: Auto-agglutination des hématies dans l'ictère hemolytique acquis. Compt. rend. Soc. de biol. de Par., 1908, lxiv, 655–657. Les ictères d'origine hémolytique. Arch. d. mal. du coeur, 1908, i, 192–231. Quoted by Krumbhaar, loc. cit., 77.
130. Willis, B. C.: Traumatic rupture of spleen; operation with recovery. Old Dominion Jour. Med. and Surg., 1914, xix, 201–205.
131. Wilson, L. B.: Pathology of splenomegaly, a study of operative and autopsy material from the Mayo Clinic. Surg., Gynec. and Obst., 1913, xvi, 240–251.
132. Winternitz, M. C.: Tuberculosis of the spleen. Arch. Int. Med., 1912, ix, 680–697.
133. Wood, H. C.: On the relation of leucocythæmia and pseudoleukæmia. Am. Jour. Med. Sc., 1871, lxii, 373. Quoted by Krumbhaar, loc. cit., 77.
134. Yates, J. L., Bunting, C. H., and Kristjanson, H. T.: The etiology of splenic anæmia or Banti's disease. Jour. Am. Med. Assn., 1914, lxiii, 2225.
135. Zaccarelli: Quoted by Krumbhaar, loc. cit., 78.

HEART

AURICULAR FLUTTER*

J. M. BLACKFORD AND F. A. WILLIUS

Sixteen cases of auricular flutter have been observed in the Mayo Clinic by us during the last thirty months. In the study of these cases a review of the literature revealed certain features which made it seem desirable to record our findings. The paucity of case reports in the literature is ample evidence that the condition is frequently overlooked.

Definition.—Auricular flutter may be described as an acceleration of the auricles to a rate beyond 200 per minute.[4] In all reported cases such acceleration has been accompanied by a partial heart block, giving a ventricular rate of one-half, one-third, or one-fourth of the auricular rate, or a total dissociation of rhythm (complete heart block); or the degree of block may vary between the auricular beats, giving a gross ventricular arrhythmia. The partial block is apparently due to the inability of the auriculoventricular bundle to conduct impulses so rapidly, or to the inability of the ventricle to respond so rapidly. There is no reason to suppose that organic disease exists in the bundle except in those few cases (two, one our own, reported to date[7]) in which there is evident complete dissociation; and in a small group of ventricular bradycardias in which the auriculoventricular bundle may at least be questioned. In the paroxysmal attacks, when the ventricles assume the full auricular rate, we have evidence of a temporary increase in irritability of the ventricle or the auriculoventricular bundle.

There is no known pathologic difference between an auricular rate of less than 200 and one at which the rate exceeds this figure, yet the clinical manifestations are so different as to justify the classification of flutter as a clinical entity.[11] The fundamental clinical differences lie in the fact that flutter tends to persist indefinitely, whereas auricular paroxysmal tachycardia rarely reaches so rapid a rate and the attack stops after a relatively short period. In flutter the auricles continue their rapid rate when the ventricles are slower, while in auricular

paroxysmal tachycardia 1–1 rhythm is always present and the sinus rhythm is restored between attacks.

Experimental.—Auricular flutter was produced experimentally by McWilliam in 1887[14] by mild faradization of the auricles of exposed animal hearts. Lewis[10] (1912–1913) observed the same condition after the intravenous injection of glyoxylic acid. Hirschfelder[5] (1908) produced it by ligation of the coronary arteries, and similar observations have been made after cooling the auricles and during chloroform anesthesia. In our laboratories, working with Kendall,[3] we produced, experimentally, hyperthyroidization in the goat by a large injection of the thyroid active principle, alpha-iodin. We have observed auricular flutter as one of the cardiac phenomena shown by practically continuous electrocardiographic tracings over several hours preceding death.

Mechanism.—Flutter is caused by focus of stimuli in the wall of the auricular muscle at a point outside the normal pacemaker or sinus node (ectopic stimuli), the discharge of stimuli being at a rate so rapid and continuous as to submerge the sinus activity. This conclusion is based on the fact that the P wave is found to have an abnormal form in the clinical electrocardiogram and that in the experimental study the P wave approaches the normal contour as the stimulus is applied nearer the sinus node.

A statement of methods by which flutter can be produced in the laboratory will help to visualize the subject. A single shock applied with the stimulating electrode to any point in the wall of the auricle causes an auricular extrasystole, providing the stimulus is applied when the muscle is not contracting. A continued mild faradization applied to the same point causes similar contractions, but each contraction is maximal, and hence only when the muscle begins to relax, or pass out of the "refractory phase," is further stimulation effective; then another contraction is caused by succeeding stimulus, etc. In other words, the auricle is contracting as rapidly as possible—a state of "flutter" during the time continuous faradization is applied.

Thus, if asphyxia is allowed to act, a visible change is found in auricular activity. Suddenly the auricle dilates and ceases coördinate contraction, but each little individual muscle bundle begins to contract regardless of the muscle mass; that is, incoördinated contraction. In other words, multiple foci of irritability occur throughout the auricular mass, due to asphyxiation. The dilated auricle as a whole is functionless. It acts only as a reservoir, but close inspection reveals the fibril-

lating muscle twitching which is characteristic of auricular fibrillation, and the total arrhythmia of the ventricular action is at once apparent.

In the human heart the irritable focus causing flutter must be the result of disease. It cannot be too strongly emphasized that flutter, per se, is only objective evidence of localized irritability in the auricular wall; and that any other organic cardiac disease may exist in the same heart.

It is evident that at present no clear distinction, mechanical or organic, can be given as differentiating paroxysmal auricular tachycardia from auricular flutter. The difference is largely a well-grounded clinical conception based on a different symptomatology. The only objective distinction is one of auricular rate, and that a partial block usually exists in flutter cases.

Pathology.—It is already evident that auricular flutter is not a pathologic entity, for we often see auricular extrasystoles, flutter fibrillation, and a sinus rhythm in a single case within a relatively short time. The literature contains only six necropsy reports in unquestioned cases; our series contains two others. Ritchie[19] has reported a lymphocytic infiltration of the epicardium, most marked in the region of the sinus node, and he thinks this may have depressed sinus activity. The cases of Gulland and Mackenzie[12] and Hume's[6] first case add nothing significant to these findings. The pathologic findings are at present unimportant, since so little has been recorded.

The irritable auricular focus is the essential feature, and our study must include all causes of localized injury or irritability to heart muscle. Such causes may be classified under three heads: (1) Infections causing localized injury; (2) general and local myocardial degeneration from any cause, as hypertension, valvular disease, goiter, etc.; and (3) localized malnutrition of the auricular wall, as in coronary sclerosis, etc.

We do not know why in certain cases a localized injury should be selected from more extensive myocardial damage to become a source of irritation, and to send forth such rapid impulses as to submerge the sinus rate and establish flutter. That such functional pathology exists, however, is evident.

We have no evidence that flutter can be purely of neurogenic origin. In all the reported cases and in our own cases there was either objective evidence of other cardiac damage or a history indicating infectious, toxic, myocardial, or coronary etiology.

Etiology.—Auricular flutter occurs four times as often in men as in

women, counting the reported cases and our own. The average age of the patients was forty-seven years, the youngest six years and the oldest eighty-two years. The condition is most frequent between the ages of forty and sixty years, but in our series more cases[3] occurred between thirty and forty years of age.

Our cases at once call attention to an etiology of infection, since antecedent diseases of probable streptococcic origin were noted with remarkable frequency, namely, 1 rheumatic fever, 5 tonsillitis, 6 bad teeth, 6 "grippe," 2 pneumonia. In 3 cases the patient dated his symptoms from one of these infections. All the patients in our series gave histories of one or more of the foregoing diseases. In 59 reported cases there are little data on this phase of the subject, but when given, the streptococcus group predominates; thirteen histories of rheumatic fever are recorded.[15, 18, 3, 9, 16, 21, 20, 19, 13] Venereal disease plays no evident part. None of our patients was syphilitic, though three cases are noted in the literature.[3, 19, 1] We noted four histories of typhoid fever; other reports contained one case.[21]

Exophthalmic goiter was definite in four of our cases and was believed to be the probable etiologic factor. One other such case is reported.[19] Mitral disease was observed in but one of our sixteen patients, though the literature[11,12,19,17,2] reports ten cases of stenotic or double mitral lesions.

Relative Incidence.—We examined electrocardiographically 3,500 patients and observed 16 auricular flutter records. There were 363 patients with auricular fibrillation, 160 showing auricular extrasystoles, 316 showing ventricular extrasystoles and 5 auricular paroxysmal tachycardia. These figures are doubtless far from a fair average, because we examined a great number of patients suffering from toxic goiter (both hyperplastic and non-hyperplastic) and fibrillation is very common in such cases. The proportion of 16 flutters to 363 fibrillations is probably a fair average.

Symptoms.—The symptoms of the condition depend essentially on the ventricular rate and the cardiac compensation. The symptoms do not depend on the auricular rate alone, for the auricles may be found at 320 and the patient may not be aware of serious trouble, or the auricles may be dilated and functionally inactive (fibrillation) yet with good cardiac compensation and with little or no discomfort. Symptoms are further confused by disease to which the flutter is incidental or terminal, as in mitral disease, arteriosclerosis, or chronic nephritis. In such cases

flutter is clearly a manifestation of serious nutritional disturbance in the auricular wall and should be regarded only as a symptom worthy of relief.

Flutter cases may be conveniently classified as paroxysmal or chronic, depending on the duration of the disorder. We use the term "paroxysmal" in cases in which the normal rhythm is restored between attacks lasting a few hours or days and "chronic" when the condition tends to persist.

Paroxysmal flutter is not clearly defined from auricular paroxysmal tachycardia, as before mentioned. We have observed it only as a disorder incidental to evident myocardial disease; it is serious because of the great strain on the myocardium. Short paroxysms of flutter occur in which the auricular rate is between 200 and 380 and the ventricular rate bears a definite or indefinite ratio to the auricular. The attack gives symptoms of cardiac embarrassment varying in degree with the cardiac compensation and the length of the attack. Palpitation, tachycardia, flushing, breathlessness, weakness, flatulence, pallor, vertigo, polyuria, faintness, and syncope come on as the attack progresses, though sudden relief may come at any time from cessation of the attack. We have seen, alternately, attacks of flutter and fibrillation in the same patient.

Chronic flutter should always be recognized, for it can usually be relieved. The flutter lasts for long periods, for weeks or even years, and can be detected by proper tracings at any time during its course. The ordinary auriculoventricular ratio is 2–1 and the pulse is usually 100 to 180, but any degree of block may exist. The pulse, therefore, may vary from idioventricular rhythm, 32, to the full auricular rate, 320.

The most constant symptoms in our cases have been persistent and obscure tachycardia and weakness. Most of the patients are subject to "weak spells"—violent paroxysmal attacks of tachycardia with acute cardiac insufficiency brought on usually by exertion and by stopping suddenly. In such paroxysms the ventricles assume or approximate the auricular rate. Certain patients have described it as "a feeling like a bird fluttering in the chest," which is probably a fairly characteristic sensation. An occasional patient is very little inconvenienced by the paroxysm and in such instances the trouble is most likely to be overlooked.

Objectively, the heart may be normal except for weak sounds and a tick-tack rhythm. Usually there is a tachycardia more or less marked,

and often there is mitral stenosis. In one-half of our cases the pulse has been regular and in the others markedly irregular, owing to regular or irregular conduction through the auriculoventricular bundle. Rapid, regular venous pulsation in the neck is indicative of the disorder; and any patient more than thirty years of age with a tachycardia unaccounted for, and particularly if he is subject to "weak spells," should be under suspicion.

Vagal Pressure.—In certain cases vagal pressure will promptly reduce the ventricular rate by increasing the degree of block; but the auricular rate is not affected by this procedure, contrasting sharply with the cases of auricular tachycardia in which sinus rhythm is suddenly restored by vagal pressure. The slowing of the ventricle is but transitory, and is recognized as due to increasing the degree of block temporarily by causing vagal depression of the auriculoventricular bundle.

The diagnosis rests finally on graphic tracings, and we believe the electrocardiograph to be far the most satisfactory. While we disclaim expert knowledge of the polygraph, we feel sure that the findings with this instrument may easily be misinterpreted and are not invariably conclusive.

SUMMARY OF CASES

Following is a brief summary emphasizing the interesting features in our cases:

CASE 119641.—A man, aged thirty-nine years, came for examination November 24, 1914. He had suffered with hay-fever for years, and with asthma during the past year. He came to the clinic during a paroxysm of tachycardia which had existed for two days. The pulse was 212 constantly, with marked evidence of cardiac embarrassment. These attacks had occurred twice within the year and had lasted six and eight days, beginning and terminating abruptly. He was unable to retain any medicine, and in spite of the treatment died on the fifth day of his attack, three days after his arrival. Before death the heart was greatly dilated and the pulse varied instantly from slow to rapid rhythm. No tracings were possible after the first day. No valvular lesion was demonstrated clinically or pathologically.

CASE 142236.—A man, aged fifty-five years, was admitted to the clinic September 28, 1915. The patient had been subject to "grippe," and five years before coming for examination had noticed dyspnea and spells of syncope with sudden onset. He would fall whenever and wherever the spells came on. At this time he rested six weeks and improved. One year later (July, 1913) he had another attack which lasted six weeks

and which necessitated two weeks in bed. April, 1914, another attack lasted a month, after which his health was good until July 7, 1915, when a sudden attack came on while he was eating supper. This had per-
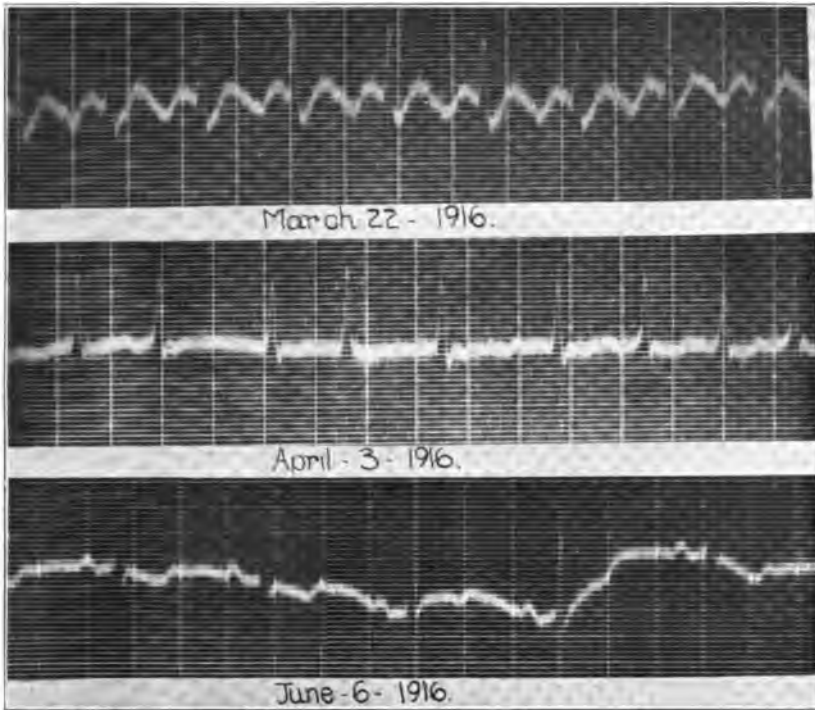
Fig. 129 (146153).—1, Typical auricular flutter; 2, fibrillation induced by digitalis; 3, normal rhythm following thyroidectomy.
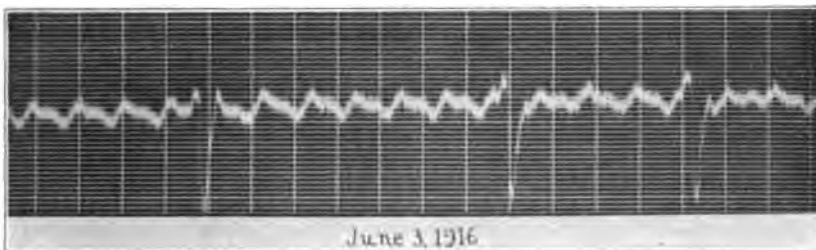
Fig. 130 (161186).—Auricular flutter with heart block; auricular rate 260; ventricular rate 43.

sisted since with violent attacks of syncope. During the first examination in the clinic the patient suddenly went into collapse. He became cyanotic, pulseless, and unconscious; there were extreme pallor and cold

sweat. Death seemed imminent, when the idea of vagal pressure suddenly occurred to one of us. Pressure on the right vagus suddenly reduced the pulse-rate (see cardiograms of similar pressure in another attack) to about 55, with prompt recovery of consciousness. Fibrillation was induced three times during two months by digitalis therapy, only to have the flutter recur after its discontinuance. The patient's fortitude in attempting a fourth course of treatment was rewarded by a return to a sinus rhythm on Christmas eve, and eighteen months later he reported that he was doing light farm work. The heart was normal objectively between attacks except for occasional auricular extrasystoles.

CASE 142802.—A woman, aged thirty-two years, was admitted to the clinic October 6, 1915. She had had repeated tonsillitis and a probable
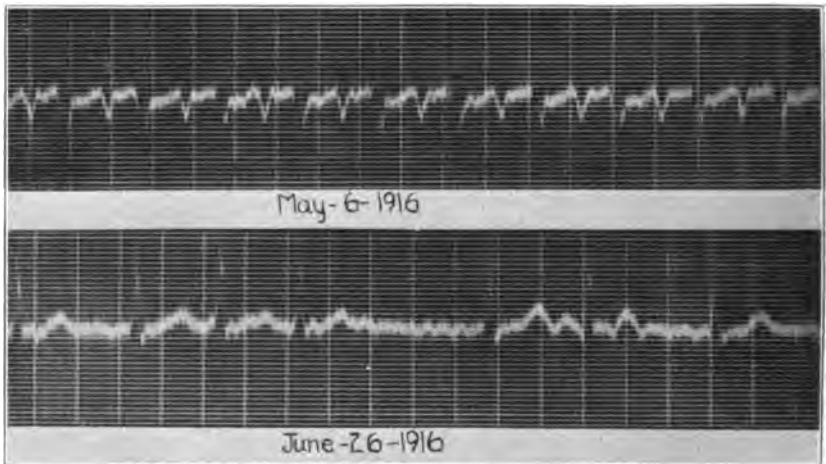
Fig. 131 (158955).—1, 2–1 flutter; auricular rate 316; ventricular rate 158. 2, fibrillation induced by digitalis.

exophthalmic goiter. She came for relief from biliary colic. For several months she had been conscious of a "fluttering heart" and had had several spells of violent palpitation, usually following exertion. Electrocardiograms showed a 320–160 rate ordinarily. While under observation she came into the office with a ventricular rate of 320 (counted by stethoscope) during a paroxysmal attack, lasting nearly two hours. She had walked several blocks to the office and was not sufficiently inconvenienced during the first hour to make complaint. The rapidity was discovered on examination, when the ventricular rate was found to have fallen to 300. She walked up one flight of stairs for a cardiographic examination during the attack, which stopped suddenly while the examination was in progress and the usual 2–1 rhythm was reëstablished. This case is unique in that it is the fastest human ventricular rate yet

recorded. The patient said she had suffered from such attacks repeatedly and that the present attack was milder than many of the others.

Under digitalis medication, fibrillation was induced, but on its withdrawal flutter returned. A second trial resulted similarly; a third attempt was made, and the patient while fibrillating was referred for cholecystectomy, which was successfully accomplished. A sinus rhythm was established some days later (rate 120) and persisted for four months, until the flutter returned following heavy work cleaning house. We obtained further tracings May 1, 1916, showing flutter, but the patient could not remain for treatment.

This case had been diagnosed as exophthalmic goiter before the patient came to us and she was anxious to have a thyroidectomy. We
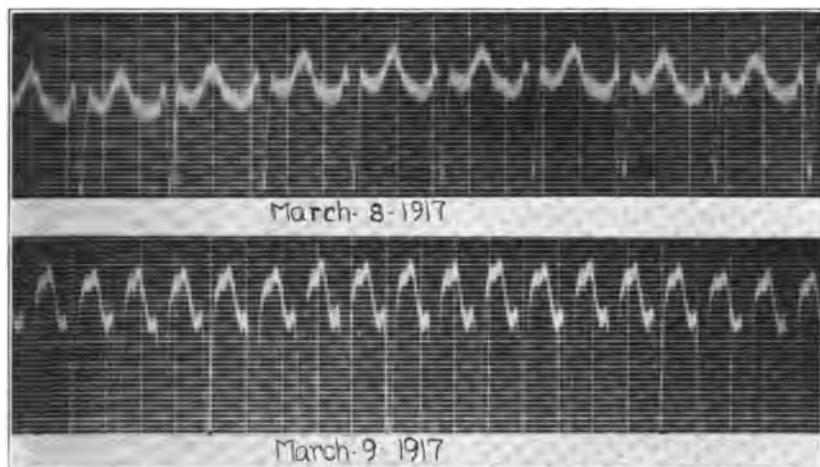
Fig. 132 (187575).—1, 2–1 flutter; auricular rate 224; ventricular rate 112; 2, paroxysm of 1–1 flutter; rate 232.

wished to defer operation on account of the heart condition and the questionable diagnosis of hyperthyroidism, and thyroidectomy was performed elsewhere (November, 1916). Pathologic examination of the tissue, which the surgeon kindly sent to us, showed the typical hyperplastic changes of exophthalmic goiter. The patient reports a pulse practically normal and health restored since operation.

CASE 145990.—A woman, aged forty-one years, came for examination March 21, 1916. The patient had had tonsillitis repeatedly. She had had the classic symptoms of exophthalmic goiter for four years. Three months previously ligations had been done in the clinic. No cardiac disorder was then suspected. On returning for thyroidectomy she was prostrated by a prolonged paroxysm of tachycardia. The cardiogram revealed flutter. She was treated with digitalis, and thyroidectomy was

done while the heart was fibrillating.   Sinus rhythm was restored soon after operation.   She gave the interesting history of a prolonged paroxysm of tachycardia the year before, during which syncope was so complete that she was thought to be dead.   August 10, 1917, the patient reported marked improvement in general health and no more spells of tachycardia.

CASE 146153.—A man, aged twenty-six years, entered the clinic March 18, 1916.   There was no history of previous infections, except typhoid in 1912.   The tonsils appeared large and unhealthy.   Classic exophthalmic goiter with symptoms had existed for nine years; relatively mild symptoms until the last two years.   He had had three spells of vomiting and prostration, probably due to flutter.   The heart action had been irregu-
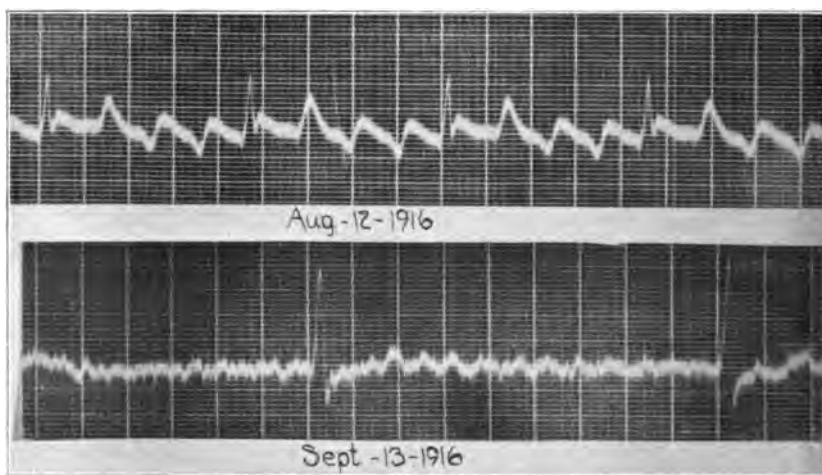
Fig. 133 (168507).—1, 4–1 flutter; 2, fibrillation with complete heart block under digitalis.

lar and rapid, but no record was taken before the ligations were done here November 26, 1915.   At the present examination the cardiogram showed typical auricular flutter.   Heavy digitalis medication, 29 c.c. in ten days, brought on fibrillation.   Thyroidectomy was performed April 10, 1917, and sinus rhythm was restored shortly after.   The patient reports, August 7, 1917, "I have forgotten all about my heart."

CASE 168507.—A man, aged forty-three years, was examined August 9, 1916.   The patient gave a history of typhoid and he was subject to tonsillitis.   He came to the clinic because of recurrent attacks of appendicitis.   He appeared healthy.   A cardiographic examination was made on account of the irregular pulse.   After discovering the flutter we elicited a good history of sudden attacks of mild syncope with rapid heart action, brought on by marked exertion during the previous five

years. Mild chronic dyspnea was also admitted. The patient was treated thirty days, taking 100 c.c. of digitol before complete heart block and fibrillation were induced. He left us then, but he has reported through his brother (August 12, 1917) that he feels well. The appendix has not been removed.

CASE 158953.—A man, aged sixty-one years, was examined May 5, 1916. Twelve months before admission, following grip and mumps, the patient had had "nervous prostration," chief symptoms, nervousness, weakness, and palpitation. His physician told him the rapid pulse was due to "nervousness." November, 1915, there was again a sudden onset of rapid heart and weakness which has persisted to date. He had "weak spells" and was dizzy. With rapidity of the heart hoarseness was no-
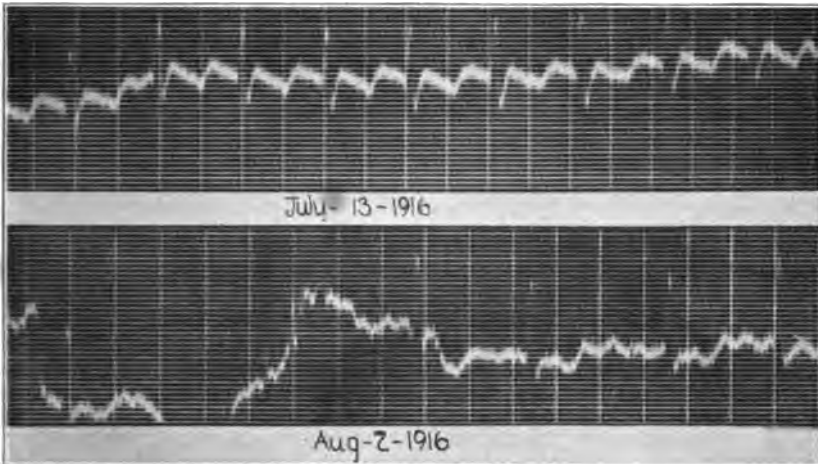
Fig. 134 (92324).—1, Auricular flutter; auricular rate 292; ventricular rate 146; 2, fibrillation induced by digitalis; rate about 120.

ticed. He was treated with 69 c.c. of digitalis twenty-three days before the onset of fibrillation. Flutter recurred and the treatment was again instituted for a few days until the onset of fibrillation. A few days later there was a second recurrence of flutter and again fibrillation was induced by digitalis. Tonsillectomy was performed July 10 without incident. The patient continued fibrillation without cardiac symptoms up to the last report. From subjective sensations he was able to say accurately whether flutter or fibrillation was present. No evidence of cardiac hypertrophy or valvular disease was obtainable at any time.

CASE 161186.—A man, aged seventy-five years, a feeble, stiff, fat old man with marked sclerosis of the peripheral vessels and evident cardiac insufficiency, was examined May 31, 1916. He dated rheumatic symp-

toms back to rheumatic fever twelve years and four years previously. Dropsy had been noted for a year, but not much dyspnea or palpitation, probably because the rheumatism made exertion difficult. Blood-pressure 170–82 and pulse varying from 44 to 68, indicating impaired auriculoventricular conduction. There was no valvular disease evident and the heart was not definitely large. Treatment by rest and digitalis at home was recommended.

CASE 92324.—A woman, aged thirty-nine years, was admitted for ex-
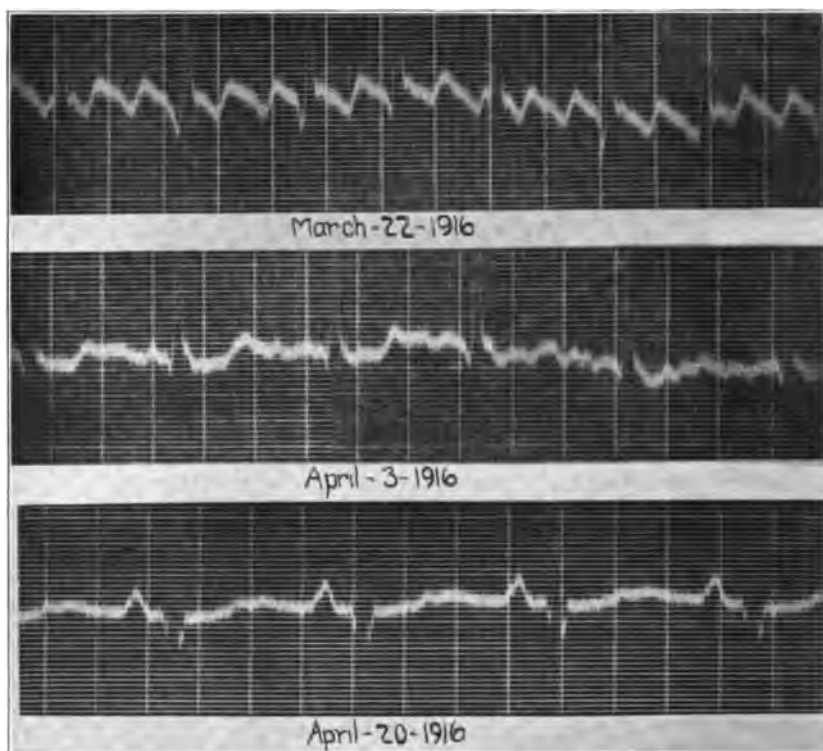
Fig. 135 (145990).—1, Auricular flutter; 2–1 rhythm; auricular rate 340; ventricular rate 170; 2, fibrillation induced by digitalis; 3, sinus rhythm following thyroidectomy; rate 92.

amination July 12, 1916. Definite exophthalmic goiter; ligation performed in the clinic October, 1913. At this time the pulse was regular, 95 to 118, and the heart greatly dilated. Thyroidectomy was performed February, 1914, after marked improvement in the heart condition. The patient returned the second time for observation. All of the previous winter she suffered from frequent colds and grip. There was no history of syncope. The first cardiogram taken showed flutter with

2–1 rhythm, ventricular rate 196. Fibrillation was readily brought on with digitalis and continued during fifty-six days of observation.
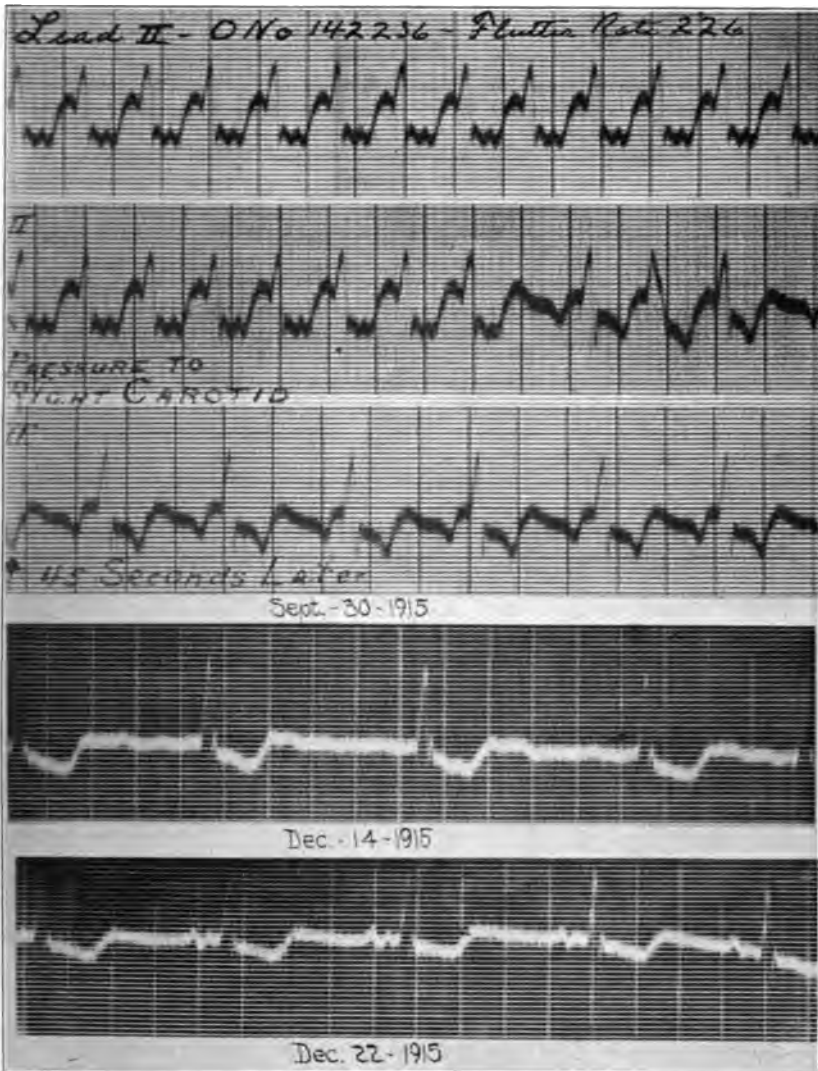
Fig. 136 (142236).—1, Paroxysm of 1–1 flutter with forty-five-second intervals between the three strips; rate 224; pressure applied to right vagus indicated by arrow at beginning of second strip; 2–1 flutter established within a few seconds, as indicated in third strip; 2, fibrillation induced by digitalis; rate, 88; 3, sinus rhythm restored; rate 71; definite abnormal auricular rate.

CASE 130119.—A man, aged fifty-two years, was admitted for examination February 17, 1917. The patient had been operated on in the

'17—27

clinic May 6, 1915, under local anesthesia for a small cyst of the tongue, but no general examination had been made at that time. The patient was very obese, with evident marked cardiac insufficiency, and the roentgen ray showed diffuse dilatation of the aorta and the heart greatly enlarged. Dyspnea had been noted for twelve years, but marked cardiac insufficiency followed grip last fall. The cardiogram showed flutter. The patient died suddenly on the fourth day in a coughing attack. Necropsy revealed a fatty, dilated heart and fatty sclerosis and dilatation of the aorta.

CASE 195883.—A woman, aged forty-three years, was admitted for examination July 1, 1917. The patient was subject to grip. She had had 10 children. The rapid heart action had been first noticed fourteen years previously during pregnancy. There had been palpitation since on exertion, and last year there were repeated spells of very rapid heart action with palpitation. Objectively the patient showed marked tachy-
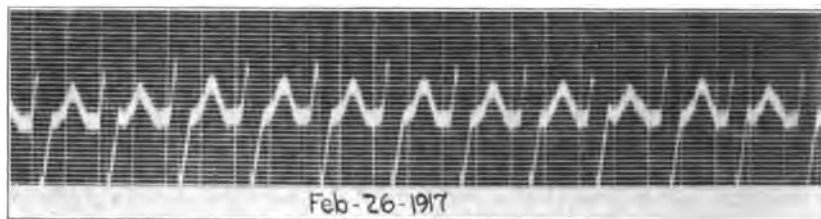
Fig. 137 (130119).—Auricular flutter; auricular rate 300; ventricular rate 150.

cardia (192). Pressure on the right vagus immediately slowed the pulse to about 60; releasing the pressure permitted the pulse to go back to 192. She was treated with large doses of digitalis, and fibrillation was brought on in a few days. Fibrillation continued since. A slower pulse is definite evidence of double mitral lesion.

CASE 187575.—A man, aged forty-five years, was admitted for examination March 8, 1917. He had had typhoid twenty-seven years previously. For two years he had been subject to attacks of dyspnea and pain in the precordium radiating to the epigastrium. Worse attacks lasted one-half hour, causing complete incapacity. The heart enlarged objectively but no valvular defect was noted. The electrocardiogram showed typical flutter, auricles 224, ventricles 112. The second examination showed ventricles 224, and a 1–1 rhythm. The patient was unable to remain for treatment.

CASE 192392.—A man, aged thirty-seven years, was admitted for examination August 25, 1917. He gave a history of a questionable sore on the penis at the age of seventeen, but we were unable to establish syphilis on a most searching investigation. Apparently the man was strong and
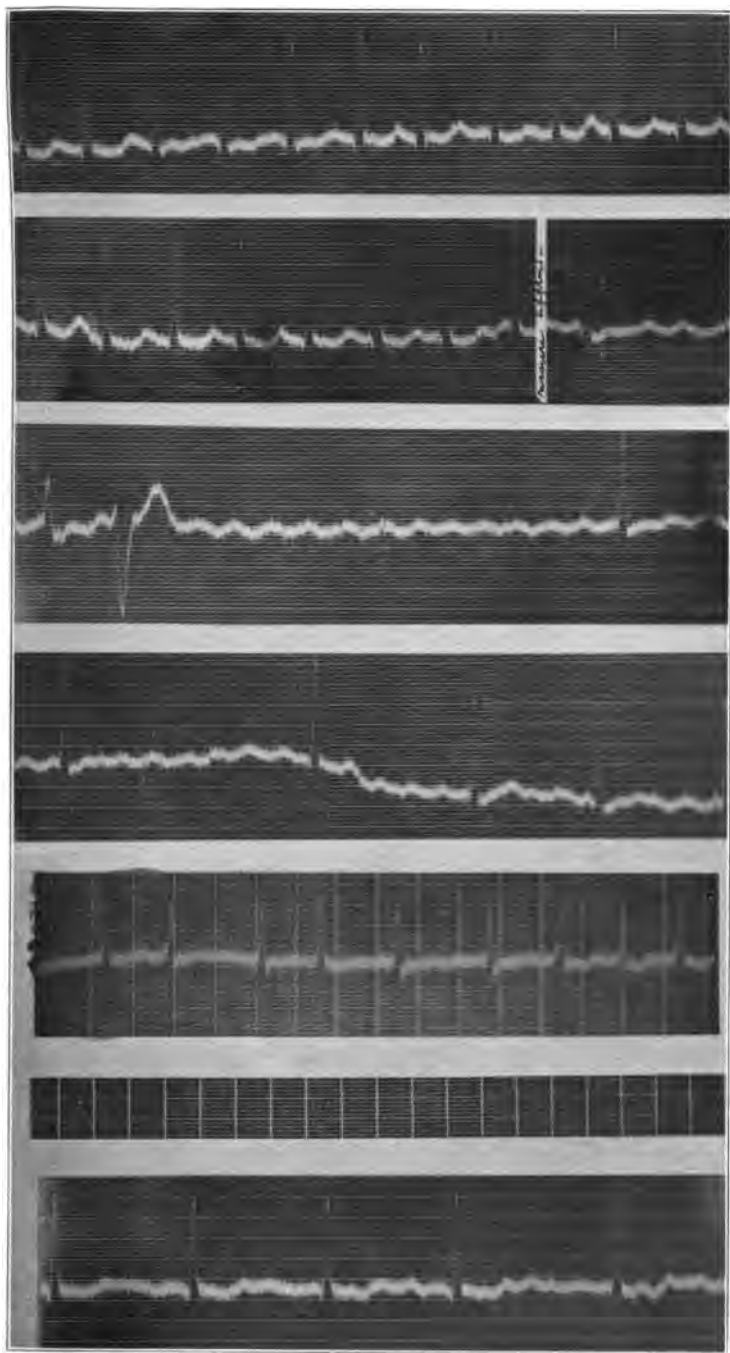
Fig. 138 (195883).—1, Auricular flutter; 2-1 rhythm. The top five strips are continuous tracings cut for reproduction. Pressure applied at point indicated by interruption of light; cessation of ventricular action 4.5 seconds in third strip on release of pressure; series of ventricular extrasystoles as shown in fifth strip before resumption of normal rhythm; 2, lowest strip shows fibrillation under digitalis.

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healthy. There had been mild dyspnea on exertion for two years, but no definite attacks. A month previously a sudden syncope followed very heavy lifting and the "right arm went dead for a little while." The heart was objectively negative except for a slow pulse (46). The electrocardiogram showed flutter, auricles 225 and ventricles 46. To rule out syphilis a therapeutic test was given, with no result after three weeks of treatment. Digitalis was started and the next morning a second cardiogram showed a sinus rhythm with complete disassociation of ventricles (46) and auricles (72). The digitalis was stopped at once. The condition had persisted since (three months). No further medication was used except potassium iodid for empirical reasons. The patient suffered no subjective inconvenience and had no evidences of a Stokes-Adams syndrome.
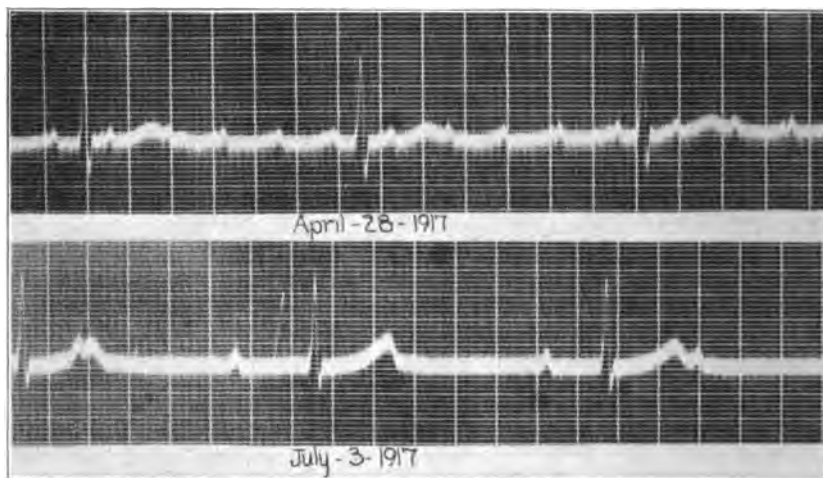
Fig. 139 (192392).—1, Auricular flutter with complete heart block; 5–1 rhythm; 2, complete heart block.

CASE 145519.—A thin, asthenic woman, aged thirty years, was admitted for examination August 2, 1917. Following pneumonia five years previously she had suffered with repeated weak spells associated with rapid heart action. The pulse was always rapid, and at the examination averaged 133. Electrocardiogram showed auricular flutter, auricles 266, ventricles 133. This patient is to return for treatment.

CASE 204974.—A man, aged thirty-seven years, was admitted for examination August 17, 1917. The patient had been asthmatic all his life, but we were unable to elicit a history of previous infection. He was a laborer and looked robust. The heart had been very rapid for three years when at work, but there was no history of weak spells. He was prepared for a cardiogram on account of irregular pulse. Auricles 258. Ventricles 172. This patient is to return for treatment.

CASE 203875.—A thin man, aged fifty-two years, was admitted for examination August 6, 1917. He was subject to colds. Eight years previously he had an attack called "bilious" for three weeks. The muscles were contracted and there were debility and weakness, with sudden onset. Morphin relieved the attack. Since then repeated lighter "bilious spells" occurred and morphin was given to prevent the
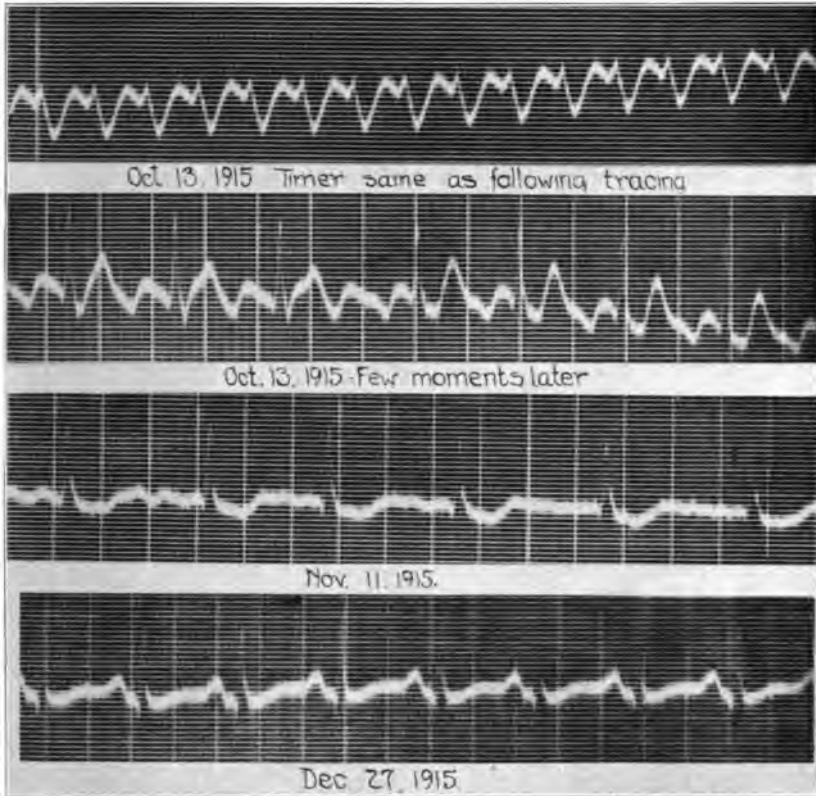
Fig. 140 (142802).—1, Paroxysm of auricular flutter, showing ventricular rate slightly above 300; timer same as next tracing; 2, a few seconds later showing break in attack during the time necessary to change plates; 3, auricular fibrillation induced by digitalis; 4, sinus tachycardia; rate 130 following cholecystectomy and tonsillectomy. This patient was operated on subsequently elsewhere for exophthalmic goiter four months after, and at present reports normal heart action and pulse-rate.

spasm. These attacks occurred at intervals of weeks or months. Podophyllum or morphin relieved the attacks. There was mild chronic dyspnea and the electrocardiogram showed flutter. The patient continued under treatment.

Treatment and Results.—As Lewis has shown, digitalis has proved to be the sovereign remedy in cases of flutter. We have used the drug

Fig. 141 (203875).—1, Paroxysm of auricular flutter, showing ventricular rate of 120; 2, twenty-six days later, showing auricular fibrillation after heavy digitalis dosage; 3, sinus rhythm five days later.

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in large doses, and have treated ten patients, not counting the two who were moribund and who died before any effect of medication was possible. Two patients (Cases 161186 and 192392) were not treated for obvious reasons, and two (Cases 204974 and 187575) were unable to stay for treatment.

The amounts of digitalis administered and a summary of the results are given in the accompanying table. All the patients were in the hospital at complete rest during the digitalis medication. Digitalis broke the flutter in all ten patients, and four finally resumed and held a normal rhythm. The others were markedly improved subjectively by the onset of fibrillation.

TABLE SHOWING AMOUNTS OF DIGITALIS GIVEN AND SUMMARY OF RESULTS

Case	Onset of Fibrillation		Onset of Toxic Effects	
	Days	Amount, c.c.	Days	Amount, c.c.
142236	75	280	51	185
142802	42	220	26	180
145990	60	94	0	0
146153	8	29	0	0
158953	51	100	22	70
922324	4	12	0	0
168507	23	100	0	0
195833	16	51	0	0
203875	24	190	22	190

The most important point in the treatment is to use enough digitalis. We have run up the dose rapidly to the physiologic tolerance of the patient. Our maximum dosage was 10.5 c.c. daily for ten days before toxic effects were evident. We have seen no bad results from such massive dosage except the temporary toxic symptoms, and we feel sure that most patients require massive dosage to obtain the desired result. Further, we have found better results from pushing the drug to physiologic complete block if the patient tolerates it to this point; that is, far beyond the point of fibrillation in most instances. In all our patients we have produced marked poisoning before discontinuing the drug. In the four cured patients we repeatedly had the fibrillation break back to a flutter until digitalis poisoning was produced.

The after-treatment is important. We discontinue medication for cured patients, but have advised in fibrillation cases that digitalis be

used, if necessary, to keep the pulse averaging below 80 when at rest. The usual general advice to cardiopaths should always be emphasized.

Operability.—One operation is reported in the literature—a death on the table under chloroform anesthesia attributed to flutter. We believe that if surgical treatment is indicated, particularly the removal of a probable source of infection or toxemia, the risk should be accepted. All operations have been performed after inducing fibrillation by digitalis and while the patient was under medication. We have been careful not to have atropin administered before operation, since this would temporarily abolish the vagus stimulation of the digitalis.

Three of our patients had exophthalmic goiter, and in two of these sinus rhythm and apparently normal health were regained after thyroidectomy. The third was a bad cardiopath, but sinus rhythm was restored, though the patient still has some symptoms of cardiac insufficiency.

Removal of the tonsils seemed advisable in cases in which there was evident focal infection, and this was done in two instances. One patient improved greatly; the other is subjectively cured. Cholecystectomy was done in one case.

SUMMARY

Auricular flutter occurs as a mechanical disorder in certain diseased hearts, and in our experience has been most frequently associated with exophthalmic goiter.

The paroxysmal attacks noted in 14 of our 16 cases are dangerous to health and even to life. Two patients died in such attacks and two others appeared so nearly dead as to deceive competent observers. The patient with flutter is always in danger of such attacks. He should always have the disorder arrested as soon as possible after its discovery.

In our experience efficient treatment may be relied on to cause the onset of fibrillation and greatly to relieve the patient. None of our patients is known to have had a recurrence of flutter after his dismissal.

Three patients were operated on under ether anesthesia for exophthalmic goiter after fibrillation was established, and one of these and one other have had tonsillectomies (local anesthesia) performed without incident. Cholecystectomy has been performed in one case.

All of the 10 treated patients are alive and much improved or cured with treatment. Five report that they cannot detect any cardiac symptoms.

REFERENCES

1. Cowan, J.: Diseases of the heart. London, Arnold, 1914, p. 205.
2. Gibson, G. A.: A discussion on some aspects of heart-block. Brit. Med. Jour., 1906, ii, 1113.
3. Gunson, E. B.: Auricular flutter followed by paroxysmal auricular fibrillation. Lancet, 1914, ii, 151–153.
4. Hertz, A. F., and Goodhart, G. W.: The speed-limit of the human heart. Quart. Jour. Med., 1908–1909, ii, 213–218.
5. Hirschfelder, A. D.: Contributions to the study of auricular fibrillation, paroxysmal tachycardia, and the so-called auriculo- (atrio-) ventricular extrasystoles. Bull. Johns Hopkins Hosp., 1908, xix, 322.
6. Hume, W. E.: A polygraphic study of four cases of diphtheria with a pathological examination of three cases. Heart, 1913–1914, v, 25.
7. Jolly, W. A., and Ritchie, W. T.: Auricular flutter and fibrillation. Heart, 1910–1911, ii, 177–221.
8. Kendall, E. C.: The isolation in crystalline form of the compound containing iodin which occurs in the thyroid; its chemical nature and physiological activity. Tr. Assn. Am. Phys., 1915, xxx, 420–449.
9. Levine, S. A., and Frothingham, C., Jr.: A study of a case of auricular flutter. Arch. Int. Med., 1915, xvi, 818–831.
10. Lewis, T.: The mechanism of the heart beat with special reference to the clinical pathology. London, Shaw, 1911, p. 311.
11. Lewis, T.: Observations upon a curious and not uncommon form of extreme acceleration of the auricle. "Auricular flutter." Heart, 1912–1913, iv, 171–216.
12. Mackenzie, J.: Diseases of the heart. Ed. 3, London, 1913, pp. 105–108.
13. Mackenzie, J.: Diseases of the heart. London, 1913, Appendix, Cases 68 and 69. Quoted by Ritchie, loc. cit. (19).
14. McWilliam, J. A.: Fibrillar contraction of the heart. Jour. Physiol., 1887, viii, 296–310.
15. Mathewson, G. D.: A case of auricular flutter. Edinburgh Med. Jour., 1913, xi, 500.
16. Neuhof, S.: Auricular flutter accompanying acute endopericarditis. Med. Rec., 1915, lxxxviii, 995–997.
17. Rihl, J.: Klinische Beobachtungen über atrioventriculäre Automatie mit Bradykardie. Ztschr. f. exper. Path. u. Therap., 1911, ix, 496–508. Quoted by Lewis, loc. cit. (11).
18. Ritchie, W. T.: Further observations on auricular flutter. Quart. Jour. Med., 1913–1914, vii, 1–12.
19. Ritchie, W. T.: Auricular flutter. Edinb., Green, 1914, p. 33.
20. Sutherland, G. A.; Auricular flutter in acute rheumatic carditis. Brit. Jour. Child. Dis., 1914, xi, 337–345.
21. Tallman, M. H.: Auricular flutter. Northwest. Med., 1916, xv, 145.

OPERATIVE RISK IN CARDIAC DISEASE*

J. M. BLACKFORD, F. A. WILLIUS, AND S. B. HAINES

General impressions of operative risk in cardiac disease are scattered throughout literature, but we have been unable to find any summary of results in a given series of cases. The failure to report such results must be due largely to two reasons: First, the difficulty of accurately classifying cardiopaths into similar groups; and, second, because in ordinary work few observers have an opportunity to study any series of such patients needing surgical treatment. These reasons are sufficient to make us feel some temerity in reporting a series of such cases, and yet we feel that such a report may throw some light on the subject.

Experience here has taught us that the best measure of operative risk in cardiac disease is a good clinical impression of the patient's ability to stand physical strain; added, of course, to a good history and a physical examination. Cases in which the heart permits the patient to go about, or in which it can be sufficiently restored by treatment to allow this, usually have been considered safe for operation. The "goiter heart," the "fibroid heart," the "prostate heart," etc., are often so remarkably improved following operation as fully to justify the risk. Cardiac disease due to focal infection, particularly tonsillitis and rheumatism, often shows the same happy result following the removal of the focus. A malignant condition complicating heart disease is considered operable if a fair hope of cure is offered, and palliative operations are often indicated in such cases. In very few instances in which there was urgent need of operation has it been refused on account of the cardiac condition, though in many the operation has been undertaken only after preliminary medical treatment. The decision in each case is based on several factors: (1) The immediate operative risk; (2) the probable improvement of the condition of the heart following operation; (3) the patient's relative chance for length of life or general health, with and without operation; and (4) in less serious conditions, whether the operative relief will justify the increased risk.

Our experience in general has justified taking risks in cases demanding surgical intervention.

A rational classification of cardiac risks on a basis of valvular disease alone is impossible. Valvular disease, with myocardial compensation sufficient to allow marked exertion, does not increase operative risk; with reasonably good compensation, allowing moderate exertion with comfort, the risk is not greatly increased, that is, a mitral stenosis may be slight and not increase the risk; with moderately good compensation the risk is not great, whereas with a very badly damaged myocardium it may be greatly increased. Similarly an aortic lesion without cardiac symptoms is easily operable, whereas the heart would not be considered operable if there was marked angina associated with the lesion. Manifestly the presence of valvular disease alone gives a poor basis for grouping similar cases.

A classification based on attempts to measure the cardiac reserve is also impossible since we have no accurate means of measuring it, and clinical impressions are variable. Angina pectoris, aortic valvular disease with pain, and aortitis with dilated aorta, are universally recognized as marked contraindications to operative interference, but the risk in such cases is variable and so few patients have been operated on that a correct statement of the risk is impossible.

Recent advances in cardiac study, particularly of the electrocardiograph, have given opportunity for better classification. We have studied results in four groups of cases of disordered cardiac mechanisms that are universally recognized as bad risks—the worst groups of risks, if we except angina pectoris and allied conditions. These groups are: (1) Auricular fibrillation; (2) auricular flutter; (3) impaired auriculo-ventricular conduction, and (4) impaired intraventricular conduction. No clinician will take exception to the statement that these disorders include the worst of cardiac risks; they give definite objective findings and are accompanied usually by extensive myocardial damage. A history showing any such cardiac disorder should always be very carefully considered.

We did not have an opportunity to examine before operation all the patients having cardiac trouble, and therefore selected only those who had had electrocardiograms taken since August, 1914. These represent the larger number of surgical cases in which cardiac disease was a complication. Undoubtedly a few patients were so obviously in a bad condition that the clinician did not consider a complete examination

necessary (that is, an electrocardiogram) and sent them home. If moribund patients and those bedridden by heart disease are excepted, our summary is a fair average of patients in whom cardiac operative risk is necessarily gravely considered. As we have mentioned, angina pectoris has not been included in the series because no evident grounds for grouping similar cases are apparent, and patients suffering severely from the condition are rarely considered operable.

AURICULAR FIBRILLATION

The mechanism of this disorder is now known to be rapid, incoordinate contractions of individual muscle-bundles of the auricular wall, that is, fibrillary twitchings, descriptively called "fibrillation." The pumping function of the auricle is lost; it becomes a dilated organ, acting only as a reservoir in the circulation. The condition is characterized in the larger number of cases by a totally arrhythmic pulse and often by a marked tachycardia. Usually fibrillation is a permanent cardiac disorder, though in a definite percentage of cases it is paroxysmal, with an established sinus rhythm between attacks.

Exophthalmic goiter.—Extensive experience with hyperplastic toxic (exophthalmic) goiter makes it evident that fibrillation is an end result of the disease toxin on the myocardium. The fibrillation is found in young patients when the toxemia is severe and has continued a long time. It is usually much less frequent under than above the age of forty.

We have recorded 9 patients under thirty years of age, the youngest twenty-one; and 12 between thirty and forty years of age, a total of 21 patients under forty years. This group comprises the worst risks. Usually the myocardiums of young patients stand strain well, yet they have given out, and this is evidence of extreme toxemia and stress. A high mortality should be expected. One patient died following a Porter hot-water injection; 3 died in from four to six weeks at home (reported as 1 cardiac death, 2 due to pneumonia); 2 died eight and fifteen months following thyroidectomy; that is, 6 of 21 patients died within fifteen months. We have recently heard from 11 of the 15 remaining patients. Five report that they are almost or completely well, and 6 report definite to marked improvement. To recapitulate, of 21 patients under forty years of age with fibrillation due to exophthalmic goiter, one-third are well, one-third are improved definitely to markedly, and one-third are dead.

In older patients—more than forty years old—it is expected that the myocardium will break down more easily, and that it will show poorer recuperative power. We have recorded 49 patients more than forty years of age with fibrillation, and have recently heard from 21 of them. Three are dead: 1 an operative mortality, 1 died six years after thyroidectomy, and fifteen months after a radical operation on the breast for carcinoma (fibrillation clinically eleven years); and 1 died in nine months from "heart failure." Eighteen of the series report as follows: 13 are much or completely relieved of cardiac symptoms; 4 are definitely improved though still cardiopaths; and 1 reports questionable improvement.

The gross operative mortality of 70 cases of fibrillation associated with exophthalmic goiter is 2 deaths, or 2.8 per cent, which compares very favorably with the present normal operative mortality of 2.6 per cent.

Thyrotoxic adenomas.—This group represents the typical "Kropfherz" of Kocher, the "goiter heart." Clinical observation has long shown that certain patients with "simple goiter" after years of good health gradually develop thyrotoxic symptoms and cardiac disease. A considerable percentage of such patients later show auricular fibrillation; in 17 cases of fibrillation there was 1 operative death and 2 deaths in nine and twenty-three months respectively. Seven other patients have been heard from; 4 are almost or completely well; 2 are definitely improved, and 1 is questionably improved.

Work on basal metabolism has shown that these patients have a constantly high metabolic rate, comparable to that of typical exophthalmic goiter. This, with the similar myocardial damage and the remarkable cardiac improvement in most cases after operation, makes the operative risk well worth while, and much less than is generally believed.

Other diseases.—There were 9 cases of fibrillation in patients less than forty years of age and 16 more than forty, a total of 25. The operations have been as follows: 9 tonsillectomies, 4 excisions of epitheliomas (2 lower lip, 1 gland of the neck, 1 larynx), 1 excision of a gland of the neck for diagnosis (sarcoma), 3 cholecystectomies and appendectomies, 3 gastro-enterostomies, 2 for ulcer, 1 for carcinomatous obstruction, 1 Talma-Morrison, 1 herniotomy, 1 cataract extraction, 1 suprapubic stab, and 1 cauterization of urethral caruncle. There were two early fatalities, one a postoperative death due to decompensation in the case of suprapubic stab, and 1 from cholangitis following a gallbladder

operation. One patient died a cardiac death nine months after tonsillectomy. Three others are dead, 1 death being reported as due to paralysis, 1 as due to peritonitis, and 1 as due to sarcoma. This makes 6 deaths in the 25 cases, only 2 of which were due to the cardiac condition. In recent reports from 11 patients all but 1 say they are definitely to markedly improved as regards the cardiac complaint. The patients who had tonsillectomies seem to have done particularly well.

AURICULAR FLUTTER

This disordered cardiac mechanism is recognized as due to the rapid coördinate contractions of the auricles, stimulated by a focus of irritations located in the auricular wall outside the normal pacemaker. The auricles contract at a rate of 200 to 380, and the ventricles usually at one-half the auricular rate, though any rhythm from a 1:1 association to complete heart block may exist. The pulse is regular in one-half of reported cases, and grossly irregular in the other half. The degree of block may vary from time to time, and most patients are subject to paroxysmal "weak spells," owing to a sudden decrease in the degree of block allowing the ventricles to assume the full auricular rate. The condition is usually chronic and may exist for years. A "weak spell" during operation is an evident danger, though we have not observed it. Four patients have been operated on, all included in the foregoing, under Fibrillation. These patients are of particular interest as apparently being the first proved cases of flutter in which operation has been done.

We have reported elsewhere[1] that these four patients were subjected to vigorous digitalis and rest treatment until fibrillation was brought on and then the operation was done. Three of the patients had exophthalmic goiter, though one had a cholecystectomy and tonsillectomy in the Clinic, and a thyroidectomy elsewhere later. One other patient had had a tonsillectomy. All the patients with exophthalmic goiter resumed a normal rhythm after operation, and two have no cardiac symptoms. The last patient (tonsillectomy) reports himself greatly improved. There has been no mortality to date.

PARTIAL OR COMPLETE HEART BLOCK

One patient with complete block has been operated on three times in eleven years—appendicectomy, amputation of breast for carcinoma, and excision of recurring skin nodules. The cardiogram was taken

before the last operation, but the pulse was remarkably slow at the former examinations. The patient is alive and reasonably well. Six patients showing delayed conduction-time between auricles and ventricles, that is, auriculoventricular intervals of 0.22 second to 0.28 second have been operated on; 3 for diseased tonsils; 1 for exophthalmic goiter, 1 for thyrotoxic adenoma, and 1 for gallbladder disease. Thus far we have no knowledge of a death in these cases. Four of the patients recently reported that they are markedly improved or cured.

Intraventricular Block

This disorder is due to impaired conduction of the cardiac impulse after it has passed the bifurcation of the auriculoventricular bundle. It is evidence of disease in the main branches of the bundle or in the subendocardial plexus, causing a slow and un-uniform diffusion of the contraction stimulus throughout the ventricular wall. Recently Oppenheimer and Rothschild[2] have excellently presented this subject, and have called attention to the serious cardiac damage and early fatality which it usually indicates. As a basis for clinical interpretation we have used for several years the same criteria which they present, and we are able to confirm their general findings in a larger series of cases (158).

The electrocardiographic curve in this condition shows a prolonged Q. R. S. complex (active ventricular phase), and variations of this up to the remarkable complexes which have been described as branch bundle defects. Undoubtedly such curves indicate extremely bad myocardial damage, as may be readily determined by ordinary clinical methods.

Relief of a probable infectious or toxic focus for the cardiac disease has seemed advisable, and operations have been done with this in view. Twelve patients have been operated on: 7 tonsillectomies, 4 thyroidectomies (3 exophthalmic goiter and 1 thyrotoxic adenoma), 1 ligation for exophthalmic goiter, and 1 salpingectomy. Six of the 7 tonsillectomy cases had histories of rheumatic fever. One patient died of cardiac insufficiency one year after tonsillectomy; 7 others (5 with definite valvular disease) report definite to marked improvement in general health. It would seem, therefore, in such cases that if a surgical condition appears as a cause or aggravation of the cardiac disease, operation should be undertaken, particularly if goiter or tonsillitis is the disturbing condition. Five of our patients were thirty years of age and two were younger, and improvement is greatly desired for such young patients.

SUMMARY

We do not believe that valvular disease with good or reasonably good compensation should be considered as a contraindication to operation, because the surgical risk is not materially increased in such cases. Careful anesthesia is, of course, essential. The record in the Mayo Clinic of 120,000 ether anesthesias with but one death under anesthesia is evidence of the remarkable safety of ether when properly administered.

The best idea of the cardiac risk in surgical cases is derived from a carefully balanced impression of the patient's general ability to stand stress. If the patient is ambulatory without marked decompensation, operation is usually safe. If marked cardiac insufficiency is evident, the patient should be medically treated until a fair degree of compensation is restored.

Surgical intervention should not be undertaken in a cardiopath unless there is definite reason to believe that the surgical relief is essential to reasonable health or will improve the cardiac condition. "Meddlesome surgery" has a fuller meaning in treating cardiopaths.

Extremely severe cardiac disease can often be definitely to completely relieved by the removal of an infectious, mechanical, or toxic source of cardiac strain or degeneration. In cardiopaths suffering from goiter the relief is often beyond all expectations. Not infrequently in such cases patients are transformed from confirmed invalids to active useful persons.

Of 100 patients operated on with auricular fibrillation, there was a gross surgical mortality of 5 per cent, but in 3 per cent only death was due to cardiac disease, or 3 per cent represents the increased risk in 100 patients. Thirteen per cent have died since leaving the Clinic; 47 others report as follows: 8 subjectively well, 20 markedly improved and able to lead fairly active lives, 16 definitely improved but still obliged to avoid exertion, and 3 report little or no improvement.

Four patients with auricular flutter were operated on after fibrillation was brought on by treatment. Two are subjectively well, and 2 are markedly improved.

Seven patients with partial or complete heart block (6 partial, 1 complete) were operated on, with no deaths. Three of the patients are markedly relieved, and 1 is unaware of cardiac difficulty at present. The complete block is unchanged.

Twelve patients with intraventricular block were operated on with the result that 1 died a year following tonsillectomy, and 7 report definite to marked improvement in spite of evident valvular disease.

We wish to emphasize that these results are given with the belief that they represent what are usually considered the worst surgical cardiopathic risks (except angina and allied conditions). With few exceptions they include all cases in the Clinic of bad cardiac disease that needed surgical treatment.

Myocardial insufficiency finally reaches a point where there is no possibility of improvement with any method of treatment with which we are familiar. We know only of the therapeutic test to determine this point in doubtful cases, and the foregoing results show that until such a stage of decompensation is reached the patient should at least be given the chance of surgery. The improvement following surgical interference in suitable cases has been so remarkable as fully to justify accepting the somewhat increased risk. The general tendency unquestionably is to overestimate the danger of operative fatality. In cases in which surgery can relieve, cardiopaths should not be refused operation, at least until a therapeutic trial has been given for the reëstablishment of some compensation.

Patients with arrhythmia, particularly fibrillation, stand operation remarkably well after medical treatment. It may be said that the fibrillating auricle has whipped the ventricle until continued ventricular action proves a reasonably good ventricular power, and life depends on ventricular, not auricular, action. Our ability to estimate operative risk depends on our ability to estimate the ventricular reserve, and remarkably little reserve seems necessary to carry the patient through good ether anesthesia. That we may err in judgment is evidenced by our three cardiac surgical deaths, and eight other deaths within a year from cardiac insufficiency. However, the general results of definite to marked improvement in about 80 per cent of suitable cases is ample justification for accepting the increased mortality.

From the foregoing study we seem justified in making the following definite conclusions: First, that many properly selected cardiopaths, often considered hopeless, may be relieved by surgical measures, and second, that the general tendency at present is to require too great a margin of cardiac safety in surgical work.

REFERENCES

1. Blackford, J. M., and Willius, F. A.: Auricular flutter. Arch. Int. Med., 1918, xxi, 147–165.
2. Oppenheim, B. S., and Rothschild, M. A.: Electrocardiographic changes associated with myocardial involvement. Jour. Am. Med. Assn., 1917, lxix, 429–431.

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PAROXYSMAL TACHYCARDIA OF VENTRICULAR ORIGIN*

F. A. WILLIUS

During the last two years an interesting group of tachycardias has been observed in the Mayo Clinic. The infrequent occurrence of these cases and the importance of their recognition merits this report. The literature contains a wealth of material dealing with tachycardia of sinus and nodal origin but few articles could be found relative to tachy-cardia having its origin in the ventricles.

The rhythmic cardiac impulse takes its origin in the sino-auricular node[3] or "pacemaker," a collection of specialized tissue lying in the sulcus terminalis at the juncture of the superior vena cava and the right auricular appendage. This has been established by the experimental work of Lewis,[6] Oppenheim and Oppenheim,[5] Eyster and Meek,[9] who found this structure to become electronegative before the rest of the sinus region. The function of "pacemaker" may be assumed by other portions of the heart, either within or outside of the conduction system, with the establishment of an ectopic rhythm.

Lewis[7] has classified these abnormal rhythms as homogenetic and heterogenetic. The former is characterized by a relatively slow rate, the onset of the rhythm is gradual, the seat of impulse production is probably always within the system of specialized tissue (conduction system), and the heart is under control of its extrinsic nerves. He believes this type to be due to exaggerated physiologic processes.

In contradistinction to this, the heterogenetic type presents a rapid pulse and rapid onset, the seat of impulse production .may be within the system of specialized tissue or without, and the heart is not under control of its extrinsic innervation. This type is believed to result only from pathologic processes.

Paroxysmal ventricular tachycardia is heterogenetic and, as far as we know, is the result of myocardial disease. The recognition of this

condition is of the utmost importance, and can be made with certainty only by means of graphic records. The introduction of the electrocardiograph has made possible the identification of obscure tachycardias.

Experimental studies have not only clarified the mechanism of this disorder, but have suggested etiologic processes. When a single induction shock is applied to any portion of the ventricle during its resting period, a single premature contraction occurs.[6] The contraction evoked is not proportionate to the stimulus applied, but always maximal,[1] constituting the well-known "all or none" law of Bowditch, and does not occur when the muscle is in the state of contraction[8] (refractory phase).

Regular series of suitably arranged induction shocks produce series of premature ventricular contractions simulating the graphic records of ventricular tachycardia. Lewis produced premature ventricular contractions by ligation of the coronary arteries constantly, by tying off the left descending branch and in most instances by impairing the circulation in the right vessel. As the nutrition of the ventricle became progressively impaired, series of heterogenetic contractions occurred, the sequence becoming longer as the nutritional changes became more marked.

By the intravenous injection of salts, Rothberger and Winterberg[11] produced this tachycardia in dogs. They found that combined stimulation of the vagi and accelerators caused cessation of the heart-beat, but after injection of 5 to 10 mg. of barium chlorid in 1 per cent aqueous solution, premature ventricular contractions occurred. With doses of 25 to 50 mg. minus accelerator stimulation, ventricular tachycardia was produced and at times a transient arrhythmia. Calcium chlorid, 100 to 200 mg. in 10 per cent aqueous solution, produced similar results. They concluded that these salts increase the ventricular irritability, but stated that the nodal tissues are not appreciably influenced. The electrocardiogram exhibits series of premature ventricular contractions, the complex forms varying with the point of origin in the ventricles. Identification of auricular contractions during the tachycardia is frequently difficult, but careful measurement shows that retrogression does not occur, as the first auricular complex of the normal rhythm falls at the proper point.

Lewis[6] maintains that the auricles and ventricles contract at the same rate, for each complex is identical to the adjacent one, and if auricles and ventricles were contracting at independent rates, the auricu-

lar complex would at times be superimposed and destroy the contour of the general curve. A case of ventricular tachycardia is reported by Palfrey, with polygraphic tracings in which the ventricular rate exceeded the auricular. This did not occur in any of the cases reported in this paper.

One other case of ventricular tachycardia is reported in the literature.[2]

Two of our cases revealed impairment of conduction, one in the junctional tissues and one beyond the main branch of the bundle of His.

Five cases of paroxysmal tachycardia of ventricular origin have come under the writer's observation during the last two years, and this disorder has occurred only in 0.047 per cent of the abnormal cases. Three cases have occurred in males and two in females—the youngest one twenty-one years, the oldest sixty-two years, with an average age of 41.4 years. Four of the patients gave definite histories of previous infection with the streptococcus group. Syphilis could not be determined in any case.

The symptomatology in all cases was strikingly uniform, all histories revealing distressing palpitation with tachycardia, induced by exertion or excitement. The paroxysms had sudden onset, stopped abruptly, and lasted from several minutes to several weeks. Vertigo attended the paroxysms in three cases and two patients complained of nervousness. Exertion dyspnea was a constant symptom. One case presented slight pitting edema of the lower extremities.

Objectively the cardiac examinations revealed little of significance. In all cases there was slight increase in the dulness to the left (one-half to three-fourths inch) and valvular disease was not demonstrated in a single instance.

The lowest pulse-rate during the paroxysms was 109, the highest 267, and the average of all recorded pulse readings was 174.

The pathologic changes in ventricular tachycardia cannot be identified as entities, as no reported cases were disclosed in a search of the literature. The experimental work of Lewis,[6] however, suggests obliterative coronary disease and its attendant nutritive changes as a hypothetic pathologic picture.

One of our patients died a suicidal death, and we were afforded the opportunity of a necropsy. The left coronary artery was distinctly atheromatous, which is very significant in view of Lewis' work. The myocardium of the ventricles presented a few areas of fibrosis, the

mitral and tricuspid leaflets were thickened, but apparently competent, and atheroma of the aortic valves was found. The thoracic and abdominal aorta were atheromatous.

In all probability any condition increasing ventricular irritability
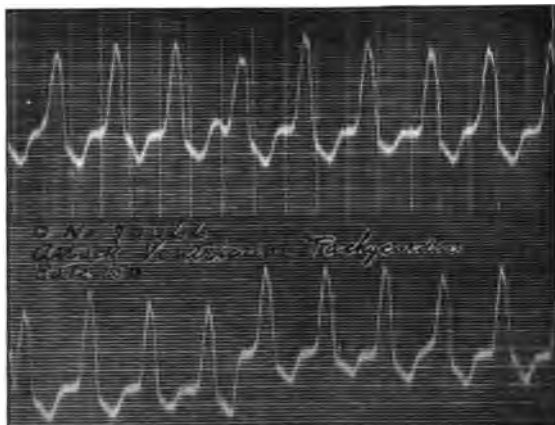
Fig 142.—No. 70066. June 28, 1915 Leads I and III. Rate 150.
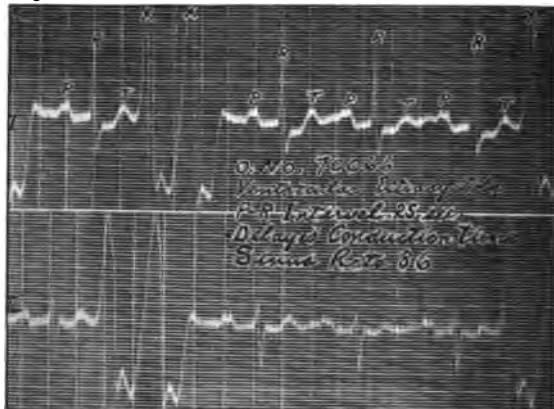
Fig. 143.—No. 70066. August 31, 1915. Leads I and III. Sinus rate 86.

is a potential factor in the production of this rare condition, and until more necropsy material is available, the conclusions as to lesion types must remain hypothetic. The gravity of the condition depends, of course, on the degree of myocardial damage and the duration of the paroxysms. One patient gave a twenty-six-year history of attacks

and the duration of paroxysms gradually increased with progressive evidence of myocardial insufficiency, the last one in which the patient was observed lasted six weeks. Cardiac reserve is, of course, the all-important factor in the consideration of heart disease and this means
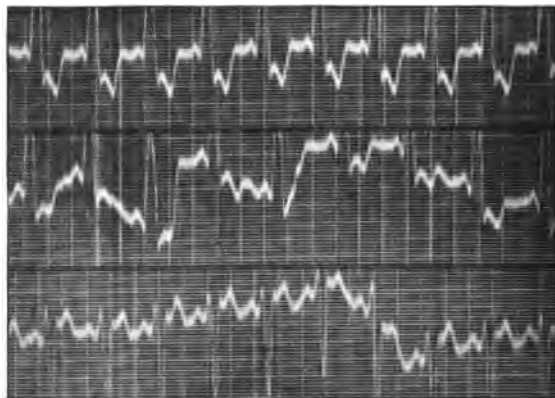
Fig. 144.—No. 185935. Feb. 19, 1917. Leads I, II, and III. Tachycardia rate 120.
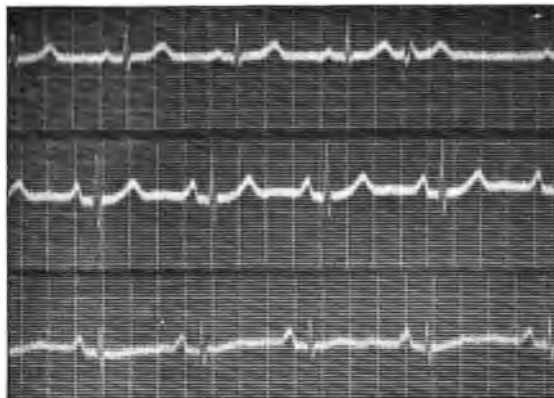
Fig. 145.—No. 194798. June 13, 1917. 9.00 A. M. Leads I, II, and III. Rate 71. Ventricular premature contractions.

largely myocardial quality. The maintenance of circulation is dependent on ventricular and not auricular action, and obviously any abnormal ventricular rhythm must be regarded as potentially a grave disorder. Lewis[4] emphasized this point, stating that ventricular tachycardia borders on fibrillation and ventricular fibrillation, as far as we know, is incompatible with life.

Little can be said relative to treatment. Two patients were treated,

both being placed on the tincture of digitalis in doses varying from 1 to 3 c.c. three times daily.   The one patient was placed at rest in bed and digitalis was administered three times to toxic effect without any change in the abnormal rhythm.   He was under observation twenty-eight days.
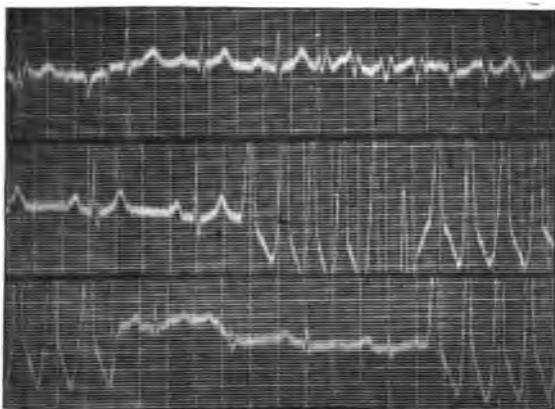
Fig. 146.—No. 194798.   June 13, 1917, 3.45 p. m.   Leads I, II, and III.   Sinus rate 80 to 109.   Short paroxysms of ventricular tachycardia rate 223 to 267.
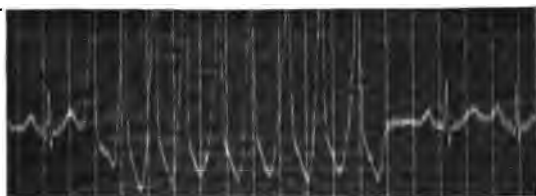
a.
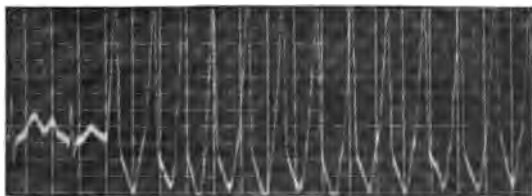
b.

Fig. 147.—*a*, No. 194798   June 13, 1917.   Lead II.   Sinus rate 100.   Tachycardia rate 200.   *b*, No. 194798. June 14, 1917.   Lead II.   Rate 220.

The other patient was symptomatically improved, but his paroxysms had never exceeded a few hours.

In cases showing evidence of myocardial insufficiency digitalis should be employed, but it is very questionable whether the abnormal rhythm

can be arrested by its administration.   In two cases vagus pressure was applied without results.   In another case the atropin test had no effect on the ectopic rhythm.

SUMMARY

1. Paroxysmal tachycardia of ventricular origin is a rare condition, occurring in only 0.047 per cent of all abnormal electrocardiograms recorded in the Clinic.
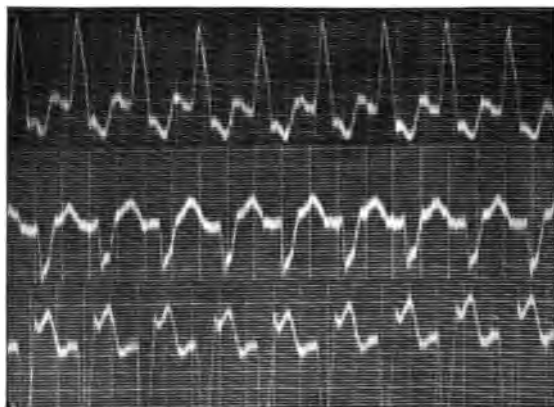
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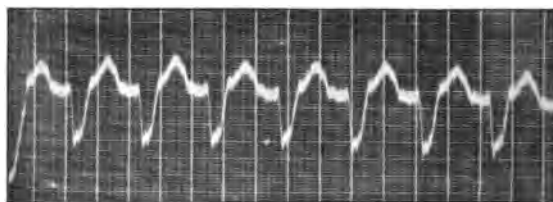
b.

Fig. 148.—a, No. 200751.   July 14, 1917.   Leads I, II, and III.   Rate 120 to 125.   b, No. 200751.   July 15, 1917.   Lead II.   Rate 125.

2. Two cases revealed conduction impairment.

3. As an etiologic factor, history of infection with the streptococcus group was elicited in four cases.

4. The symptomatology in all cases was very uniform, palpitation, tachycardia, and exertion dyspnea being complained of by all the patients.   Vertigo attended the paroxysms in three cases.

5. The average pulse-rate during the paroxysms was 174.

6. One case coming to necropsy revealed distinct atheroma of the left coronary artery, which is very significant.

a.

b.

c.
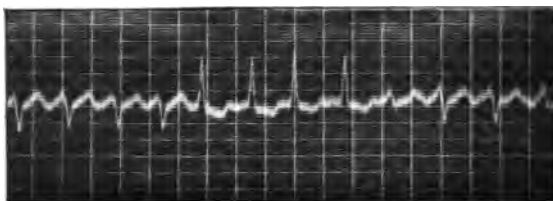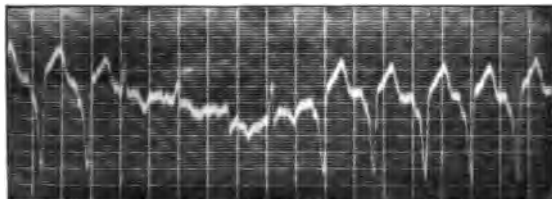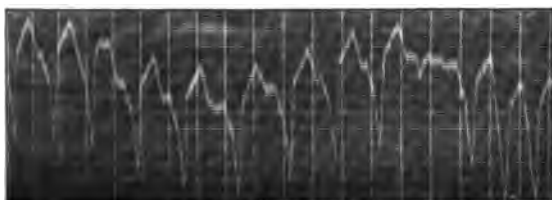
Fig. 149.—*a* No. 98618. July 25, 1917. Lead II. Rate 172. Occasional nodal complexes. *b*, No. 98618.
July 25, 1917. Rate 172. *c*, No. 98618. July 25, 1917. Lead III. Rate 172.
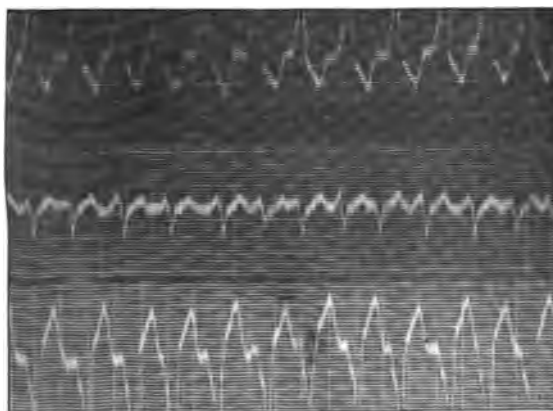
Fig. 150.—No. 98618. July 26, 1917. Leads I, II, and III. Rate 169 to 180.
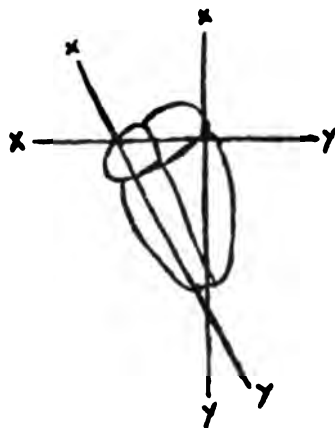
Fig. 151.
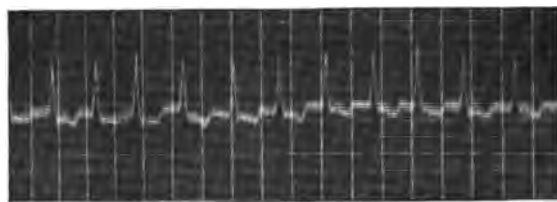
a.
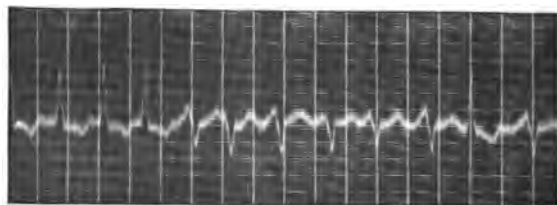
b.

Rate 150   Rate 166
c.

Fig. 152.—a, No. 98618.   July 28, 1917.   Lead II.   Rate 150. Nodal tachycardia.   b, No.   8618.
July 28, 1917.   Lead II.   Rate 175.   Nodal and ventricular tachycardia.   c, No. 98618.   July 28, 1917.
Lead II.   Failure of vagus pressure

7. As life is dependent on ventricular and not on auricular action, this condition must be considered potentially grave.

8. Digitalis medication in two cases treated did not affect the abnormal rhythm.

CASE 1 (70066).—A male, sixty-two years of age, came to the Clinic June 28, 1915. Five-year history of paroxysms of rapid pulse and palpitation. This case not only presents coupled heterogenetic ven-

a.
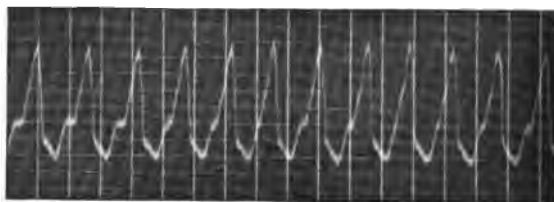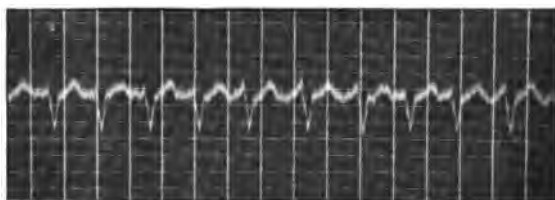
b.
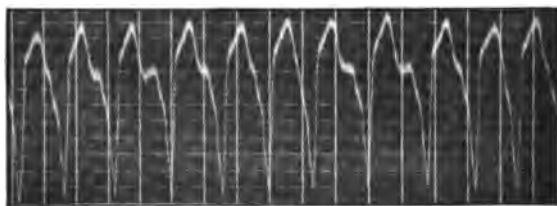
c.

Fig. 153.—a, No. 98618.   August 1, 1917.   Lead I.   Rate 192.   b, No. 98618.   August 1, 1917.   Lead II. Rate 175.   c. No. 98618.   August 1, 1917.   Lead III.   Rate 180.

tricular contraction and short paroxysms of ventricular tachycardia, but also impaired conduction through the junctional tissues, the pulse-rate interval being 0.25 second. There is hypertrophy of the left ventricle. The sinus rate is 86; the ventricular tachycardia rate is 150 (Figs. 142 and 143).

CASE 2 (185935).—A female, twenty-one years of age, came to the Clinic February 17, 1917. Three-year history of palpitation and tachy-cardia. Ventricular tachycardia. Rate 120. In this instance the

auricular complexes are evident and have the same rate as the ventricular. There is marked hypertrophy of the left ventricle (Fig. 144).

CASE 3 (194798).—A male, forty-two years of age, came to the Clinic May 5, 1917. Two-year history of spells of palpitation and tachycardia. Electrocardiograms show short paroxysms of ventricular tachycardia with intervening sinus rhythm (Figs. 145, 146, and 147).

CASE 4 (200751).—A female, forty-four years of age, came to the Clinic July 11, 1917. Six-week history of palpitation and tachycardia. Ventricular tachycardia with rates varying from 120 to 125. At times the auricular complexes can be identified. This case presents evidence of arborization block (Fig. 148).

CASE 5 (98618).—A male, thirty-eight years of age, came to the Clinic July 25, 1917. Twenty-six-year history of paroxysms of palpitation and tachycardia, increasing in frequency and duration. This case presents several interesting features. Occasional complexes are seen arising, probably in the junctional tissues. There is a constant difference in the general appearance of Lead II from all the other cases, and probably it can be explained by the point of origin of the ectopic impulses. They arise from the basal portion of the left ventricle and from the direction of the heart's axis; Lead II transects chiefly the "action currents" of the right heart. (See Fig. 151.) The lines x–y represent the transecting planes (Leads) by which the lines of force (action currents) are cut. Figure 152 shows the failure of vagus pressure to affect the tachycardia. A marked arrhythmia is present at times and probably signifies variation in velocity of impulse discharge (Figs. 149, 150, 151, 152, and 153).

REFERENCES

1. Bowditch, H. P.: Ueber die Eigenthümlichkeit der Reizbarkeit, welche die Muskelfasern des Herzens zeigen. Arbeiten aus d. physiol. Anst. z. Leipzig, 1869 (published in 1872), 139–176.
2. Hart, T. S.: Paroxysmal tachycardia; the paroxysms arise from the impulses of ventricular origin; the auricle responds to the ventricle; evidence of two points of abnormal ventricular irritability. Heart, 1912–1913, iv, 128–134.
3. Keith, A., and Flack, M.: The form and nature of the muscular connections between the primary divisions of the vertebrate heart. Jour. Anat. and Physiol., 1906–1907, xli, 172–189.
4. Lewis, T.: The experimental production of paroxysmal tachycardia and the effects of ligation of the coronary arteries. Heart, 1909–1910, i, 98–137.
5. Lewis, T., Oppenheim, B. S., and Oppenheim, A.: The site of origin of the mammalian heart-beat; the pacemaker in the dog. Heart, 1910, ii, 147–169.
6. Lewis, T.: Mechanism of the heart beat. London, Shaw, 1911, 37, 136, 158.
7. Lewis, T.: Exceptional types of slow heart action. Quart. Jour. Med., 1912–1913, vi, 221–235.
8. Marey, E.: Recherches sur les excitations electriques du colur. Jour. d. l'Anat. e. d. Physiol., 1877, xiii, 60–83.
9. Meek, W. J., and Eyster, J. A. E.: Experiments on the origin and propagation of the impulse in the heart. Am. Jour. Physiol., 1914, xxxiv, 368–383.
10. Palfrey, F. W.: Paroxysmal tachycardia confined to the ventricles or to the auricles, with illustrative cases. Med. and Surg. Rep. Bost. City Hosp., 1913, 16. s. 182–189.
11. Rothberger, C. J., and Winterberg, H.: Über die experimentelle Erzeugung extrasystolischer ventrikulärer Tachykardie durch Acceleransreizung von Barium and Calcium. Arch. f. d. ges. Physiol., 1911, cxlii, 461–522.

BLOOD

THE FACTORS OF COAGULATION IN THE BLOOD IN CERTAIN PATHOLOGIC CONDITIONS*

DOROTHY FOSTER PETTIBONE

Elaborate studies have been made in the past on the various factors which concern the coagulation of blood. Howell[7] has outlined minutely the individual constituents and their respective functions in normal blood. According to Howell, there are five factors in coagulation, that is, prothrombin, fibrinogen, calcium salts, thromboplastin, and anti-thrombin, all of which may show variations in disease. These are all normally present in the circulating blood except thromboplastin, which is contained in all tissue-juices as well as in the formed elements of the blood. On injury of the vessel, therefore, thromboplastin is liberated from the surrounding tissue and the platelets and frees the blood of antithrombin, allowing the prothrombin to act with calcium and the thrombin to unite with fibrinogen and form fibrin. According to Morawitz (quoted by Drinker and Hurwitz[3]), thrombokinase transforms thrombogen, which normally circulates in the blood, to prothrombin. Prothrombin is then changed to thrombin by calcium salts. Thrombin reacts with fibrinogen and produces fibrin. Thrombogen has not been differentiated in any way from prothrombin.

Since the common acceptance of these underlying principles, much work has been done on these same factors in various pathologic conditions with special reference to hemorrhagic disturbances. Methods have been devised whereby these separate factors may be isolated and quantitatively estimated. I have studied a group of cases with special emphasis on prothrombin, calcium salts, and platelets. Among these 45 cases are 2 of hemophilia, 7 of myelogenous leukemia, 2 of purpura, 9 of epilepsy, 12 of jaundice (10 obstructive and 2 hemolytic), and 13 of a miscellaneous group.

HEMOPHILIA

Many workers have reported observations on the blood of hemophiliacs, and the facts they note have agreed for the most part. Howell[8] in his prothrombin tests proved that one may by this comparative method readily distinguish between hemophilic and normal bloods. Sahli believes that the condition is due to deficient thromboplastic material, but there has been suggested as yet no satisfactory method for determining the amount of this substance. The method I have used for determining prothrombin time is that of Howell[8]: Draw 8 c.c. of blood into a sterile syringe, previously rinsed out with normal salt solution, and express into a tube containing 1 c.c. of a 1 per cent potassium oxalate. Invert the tube once to mix thoroughly and centrifugalize for fifteen minutes. In a series of small tubes place graduated amounts of 0.5 per cent calcium chlorid, beginning with 2 drops and stopping at 8 drops. Add to each tube 5 drops of the plasma and take time of coagulation.

TABLE 1

	TUBE 1	TUBE 2	TUBE 3	TUBE 4	TUBE 5	TUBE 6	TUBE 7
Calcium chlorid......	2 drops	3 drops	4 drops	5 drops	6 drops	7 drops	8 drops
Plasma.............	5 drops	5 drops	5 drops	5 drops	5 drops	5 drops	5 drops
Normal prothrombin time..............	6 min.	8 min.	8 min.	10 min.	10 min.	12 min.	14 min.

We know by this test that in hemophilias the prothrombin-antithrombin balance is upset, but it is not certainly proved that it is the actual amount of prothrombin that is altered. Addis[1] believes the prothrombin to be present in normal amounts in these cases, but it is so altered as to require longer time for activation to the thrombin present. An excess of antithrombin is present only as a result of decreased prothrombin.

The coagulation time of hemophilia is always long. In estimating this time accurately there are many difficulties to consider. The method used is that described by Lee and White.[10] One c.c. of blood is drawn from the vein into a sterile syringe previously washed with normal salt solution, and expressed into a Wassermann tube which has also been rinsed with normal salt solution. Care must be taken to leave salt solution in the needle before puncture, as the admission of air-bubbles greatly hastens the coagulation of the blood. The needle is removed so

as not to break up the platelets in expressing the blood, and the tube is rotated endwise every thirty seconds until the clot adheres to the tube when inverted. Cohen[2] has shown how necessary are absolute cleanliness, uniformity of apparatus, exact amount of blood, and constant temperature.[11] The time of coagulation greatly depends on the extent of contact to the glass; it may be greatly hastened by any shaking of the tube. Hemophilic blood may become gelatinous in a comparatively short time, but it is easily noted that the clot is not firm, and that its disturbance results in its breaking down. Minot and Lee[13] found that the clots often formed as quickly as normal, but never became as firm. If this first clot is removed, a second clot will form; this is also an imperfect clot, and may be removed. It has been observed recently by Lee, but not as yet published, that six and eight clots can be removed in succession from the blood of hemophiliacs, while a normal blood will seldom form a second clot. I was able to remove four clots from the blood in one case, while in normal controls I have never removed more than two.

CASE 185593 is worthy of special attention. This patient had a definite history of familial hemophilia; his coagulation time was exceedingly long, but his prothrombin time was within normal limits and his platelet count was 115,000 per c.mm. His mother's blood was then examined and found to have an exceedingly long prothrombin time, though a normal coagulation time. When the prothrombin time was determined, the material was invertible, though not as solid and set as in normal serums. Workers in this country have been looking for just such findings, but have not made the actual observations.

CASE 182535.—In this case there was a coagulation time of seventy-three minutes, and after transfusion the coagulation time was reduced to thirty-four minutes. The prothrombin time was not estimated because of difficulty in procuring blood.

Wright has attributed the hemophilic condition to a calcium deficiency. Hurwitz and Lucas,[9] in studying five cases in detail, observed the characteristic delay in coagulation and a constant deficiency in prothrombin; other factors of coagulation, however, were present in normal amounts. In the case shown in Table 2 no appreciable difference in the amount or activity of calcium was observed.

EPILEPSY

The results of numerous observations on the blood of patients with epilepsy have been fairly uniform, with the exception of the results concerning coagulation time, and these have been most varied. It has

'17—29

TABLE 2.—HEMOPHILIA

CASE	PROTHROMBIN TIME (CALCIUM CHLORID, 0.5 PER CENT)							COAGULATION TIME	CALCIUM TIME	PLATELET PER C.MM.
	2 drops	3 drops	4 drops	5 drops	6 drops	7 drops	8 drops			
183593	0	0	12 min.	10.5 min.	10.5 min.	10 min.	..	93 min.	3 hrs. (imperfect clot)	115,000
			Twenty-four hours after transfusion:							
Mother of patient	99 min.	99 min.	75 min. Lost	25 min.	28 min.	39 min.	..	10 min.	12 min.	171,000
						87 min. (imperfect clot throughout)		8 min.	11.5 min.	202,000

TABLE 3.—EPILEPSY

CASE	PROTHROMBIN TIME (CALCIUM CHLORID, 0.5 PER CENT)							COAGULATION TIME	CALCIUM TIME	PLATELET COUNT
	2 drops	3 drops	4 drops	5 drops	6 drops	7 drops	8 drops			
184006	..	Not done		..	..	..	..	11 min.	Not done	Not done
185070	..	Not done		..	..	..	..	7 min.	5 min.	Not done
186346	..	Not done		..	..	..	..	6 min.	4 min.	Not done
186105	0	26 min.	25 min.	26 min.	27 min.	..	..	8 min.	14 min.	Not done
188502	0	19 min.	15 min.	15 min.	16 min.	..	..	12 min.	8 min.	Not done
189352	8 min.	8 min.	8 min.	7 min.	7 min.	..	..	9 min.	10 min.	Not done
191596	10 min.	10 min.	10 min.	9 min.	9 min.	9 min.	9 min.	4 min.	4 min.	178,000 per c.mm.
186248	..	Not done		..	..	..	..	15 min.	Not done	Not done
192424	6 min.	7 min.	8 min.	8 min.	9 min.	9 min.	9 min.	6 min.	5 min.	215,000 per c.mm.

been found by several workers to be greatly shortened, while Turner believes the time to be greater in cases of epilepsy. Thorn[14] reports a series of 203 patients with epilepsy whose coagulation time he determined in the method outlined by Lee and White.[10] Ninety-two per cent of these patients fell within normal limits, 5.5 per cent fell under the minimum, and 2.5 per cent were over the maximum. Two and one-half to fourteen minutes marked the extremes of the series. Using the same method for determining coagulation time, I studied a series of 9 patients presenting a range of from four to fifteen minutes, while controls of normal persons ranged from four to twelve minutes.

It seems reasonable to conclude that there is no change in the coagulation time of the blood of patients with epilepsy. A great deal depends on the technic, and the differences occurring among normal persons vary in a similar manner.

It is believed that patients with epilepsy may be benefited by calcium lactate. Two patients have returned after a period of from six weeks to two months of the administration of calcium, and were found to have enough calcium in the blood to produce coagulation in less time than by the addition of calcium chlorid (Table 3).

HEMORRHAGIC PURPURA

It has been noted by many that the normal retractability of the blood-clot depends on the presence of platelets. Duke[4] proved experimentally that platelets may leave behind them the power to clot, but must be present to produce retraction of the clot. I have noted two cases in which the platelet count was 14,000 per c.mm. and no retraction of the clot occurred in eighteen hours. They were typical cases in all respects.

TABLE 4

CASE	PROTHROMBIN TIME (CALCIUM CHLORID, 0.5 PER CENT)							COAGULATION TIME	CALCIUM TIME	PLATELET PER C.MM.
	2 drops	3 drops	4 drops	5 drops	6 drops	7 drops	8 drops			
191562	5 min.	5 min.	6 min. Not taken	6 min.	8 min.	10 min.	10 min.	5 min.	5 min.	14,000
157449	5 min. After transfusion:							3 min.	3 min.	14,000
										199,000

Hurwitz and Lucas[9] are convinced that the chronic purpuras do at times present abnormalities other than platelet deficiency. In two patients under their observation for more than six months they noted fluctuations in the amount of circulating antithrombin. I have not estimated antithrombin in any of my series.

JAUNDICE

It has long been an established fact that in certain types of jaundice there is a definite delay in coagulation-time. Morawitz and Bierich believed that the altered coagulation-time was independent of the intensity of the jaundice. Lee and Vincent[11] note that this delayed coagulation does not show up until five or six weeks after the onset of jaundice. The good effects of calcium treatment are felt after several days, and the case is deemed safely operable when the calcium-time reaches seven minutes. This time is estimated according to Lee and Vincent's[11] technic. One c.c. of the patient's blood is drawn into a sterile syringe previously rinsed with salt solution, and expressed, without the needle, into a small tube containing six drops of a 0.5 per cent calcium chlorid solution. The tube is inverted every thirty seconds and the calcium time is taken at the point of coagulation. The test is the same as for coagulation time, with the addition of calcium chlorid. It has been found that too much as well as too little calcium will serve to delay the process of coagulation.

Blood-platelets were isolated in such cases by Lee and Vincent, and were found to act normally both in the formation and retraction of the clot.

It has been found experimentally that bile has an inhibitory effect on the formation of thrombin. Bile will entirely prevent coagulation in vitro even in the presence of the optimum amount of calcium. It is probable, however, that bile never becomes so concentrated in the blood of jaundiced patients (Tables 5 and 6).

MYELOGENOUS LEUKEMIA

Little note has been taken in this connection of the blood of myelogenous leukemia. In my series of seven patients it will be seen that there is present a tendency to prolonged prothrombin times although the coagulation times are quite short. Cohen[2] has shown experimentally that a marked leukocytosis very definitely delays coagulation.

It is evident that these patients have the optimum amount of cal-

TABLE 5.—OBSTRUCTIVE JAUNDICE

CASE	Prothrombin Time (Calcium Chlorid, 0.5 Per Cent)							Coagulation Time	Calcium Time	Platelet per c.mm.
	2 drops	3 drops	4 drops	5 drops	6 drops	7 drops	8 drops			
160395 Carcinoma	8 min.	10 min.	10 min.	10 min.	10 min.	13 min.	13 min.	8 min.	5 min.	212,000 per c.mm.
183889 Traumatic	19 min.	20 min.	20 min.	21 min.	34 min.	15 min.	...	15 min. After calcium treatment 12 min.	11 min. 20 min.	203,000 per c.mm.
189394 Gallstones	30 min.	16 min.	15 min.	16 min.	16 min.	...	...	4 min.	6 min.	258,000 per c.mm.
190480 Carcinoma	13 min.	11 min.	11 min.	11 min.	9 min.	10 min.	11 min.	10 min.	6 min.	212,000 per c.mm.
125271 Traumatic	5 min.	5 min.	5 min.	6 min.	6 min.	7 min.	8 min.	5 min.	5 min.	194,000 per c.mm.
192733 Gallstones	6 min.	6 min.	6 min.	9 min.	9 min.	9 min.	9 min.	8 min.	8 min.	262,000 per c.mm.
194975 Traumatic	21 min.	19 min.	18 min.	16 min.	18 min.	20 min.	24 min.	21 min. (2 clots)	14 min.	209,000 per c.mm.
96625 Carcinoma	0	36 min.	25 min.	18 min.	19 min.	20 min.	...	20 min.	8 min.	208,000 per c.mm.
190648 Abscess from ruptured gallbladder	9 min.	8 min.	7 min.	7 min.	7 min.	9 min.	9 min.	4 min.	6 min.	210,000
192750 Gallstones	10 min.	10 min.	13 min.	15 min.	15 min.	16 min.	18 min.	9 min.	12 min.	228,000

TABLE 6.—HEMOLYTIC JAUNDICE

Case	Prothrombin Time (Calcium Chlorid, 0.5 Per Cent)							Coagulation Time	Calcium Time	Platelet Count
	2 drops	3 drops	4 drops	5 drops	6 drops	7 drops	8 drops			
192817	9 min.	9 min.	10 min.	13 min.	14 min.	14 min.	15 min.	14 min.	17 min.	131,000
190364	5 min.	7 min.	7 min.	7 min.	7 min.	9 min.	9 min.	9 min.	5 min.	200,000

TABLE 7.—MYELOCYTIC LEUKEMIA

Case	Prothrombin Time (Calcium Chlorid, 0.5 Per Cent)							Coagulation Time	Calcium Time	Platelet Count
	2 drops	3 drops	4 drops	5 drops	6 drops	7 drops	8 drops			
192443	7 min.	7 min.	8 min.	9 min.	9 min.	9 min.	10 min.	8 min.	12 min.	196,000
192150	16 min.	13 min.	12 min.	12 min.	12 min.	14 min.	14 min.	8 min.	8 min.	194,000
177183		Not done						12 min.	14 min.	270,000
176684	17 min.	13 min.	13 min.	2 hrs.	2 hrs.			8 min.	9 min.	185,000
186558	14 min.	12 min.	13 min.	15 min.	15 min.			8 min.	11 min.	Too many myelocytes
162899	15 min.	Not done	20 min.	20 min.	20 min.	21 min.	25 min.	18 min.	16 min.	280,000
180499								7 min.	0 min.	188,000

cium, as the addition in vitro of three drops of calcium noticeably delays coagulation (Table 7).

MISCELLANEOUS CASES

Drinker and Hurwitz[3] found prothrombin to be slightly diminished in all patients with pernicious anemia. I found that to be true in the one patient examined in the Mayo Clinic. The platelet counts are, however, relatively normal.

Three of the splenomegaly cases presented delayed prothrombin times. Coagulation times were rather long, but the addition of calcium tended to retard.

Among this miscellaneous group there were several types of conditions. As control cases, they showed nothing abnormal in their factors in coagulation (Table 8).

NOTES ON TECHNIC

In doing these prothrombin tests we have noted that on reducing the amount of blood used to just one-half, the results were identical and the test more economical, the amount of potassium oxalate being reduced proportionately. Care must be taken to use the same needle for measuring calcium and serum, for the time varies appreciably if the size of the drops is not uniform. I have also done parallel prothrombin tests on several cases, using 0.5 c.c. of potassium oxalate to 8 c.c. of blood. In the cases of jaundice great difficulty was experienced in avoiding a clot while centrifugalizing the blood. If a clot had formed, the serum it expressed would not clot on the addition of calcium. In the cases in which the serum did not clot while spinning, however, a shorter prothrombin time was manifested when only 0.5 c.c. of oxalate was used. In these cases there was not sufficient oxalate to precipitate all the calcium, and in one case there was so much native calcium that the optimum amount of calcium brought the shortest time of clotting in the first tube, followed by an excess of calcium in the rest of the tubes, and a consequent retarding of the clotting process.

The method employed for platelet enumeration is that described by Wright and Kinnicutt.[16] Blood was mixed with the diluting fluid in the proportion of one to a hundred by means of the ordinary red blood-corpuscle pipet and counted in the blood-counting chamber with a high dry objective. The diluting fluid consisted of two parts of an aqueous solution of brilliant cresyl blue (1 : 300) and three parts of an aqueous

TABLE 8.—MISCELLANEOUS

Case	Prothrombin Time (Calcium Chlorid, 0.5 Per Cent)							Coagulation Time	Calcium Time	Platelet Count
	2 drops	3 drops	4 drops	5 drops	6 drops	7 drops	8 drops			
183556 Diabetes	30 min.	23 min.	16 min.	17 min.	11 min.	15 min.	..	4 min.	..	..
76654 Splenic anemia (?)	0	40 min.	25 min.	25 min.	23 min.	..	..	16 min.	22 min.	288,000 per c.mm.
192553 Splenic anemia	11 min.	13 min.	14 min.	15 min.	15 min.	17 min.	19 min.	9 min.	10 min.	177,000 per c.mm.
192503 Cirrhosis of liver (?) with splenomegaly	7 min.	9 min.	9 min.	12 min.	14 min.	18 min.	18 min.	10 min.	13 min.	..
190774 Localized tuberculous splenomegaly	9 min.	8 min.	7 min.	7 min.	7 min.	7 min.	8 min.	7 min.	6 min.	197,000 per c.mm.
192719 Pernicious anemia	14 min.	20 min.	22 min.	24 min.	30 min.	30 min.	30 min.	5 min.	4 min.	204,000 per c.mm.
185197 Pernicious anemia	..	..	Not done		..	..	..	6 min.	Not done	157,000 per c.mm.
189232 Lues II	..	..	Not done		..	..	..	Not done	Not done	269,000 per c.mm.
193565 Polycythemia	8 min.	8 min.	7 min.	6 min.	6 min.	6 min.	6 min.	8 min.	9 min.	115,000 per c.mm.
190423 Migraine	8 min.	8 min.	8 min.	7 min.	7 min.	9 min.	9 min.	7 min.	9 min.	208,000 per c.mm.
191091 Biliary cirrhosis (?)	17 min.	17 min.	16 min.	16 min.	16 min.	16 min.	16 min.	15 min.	10 min.	223,000 per c.mm.
192121 Biliary cirrhosis (?)	5 min.	5 min.	5 min.	5 min.	5 min.	6 min.	6 min.	7 min.	8 min.	255,000 per c.mm.
194103 Hypernephroma	10 min.	12 min.	14 min.	16 min.	15 min.	15 min.	16 min.	9 min.	8 min.	200,000 per c.mm.

solution of potassium cyanid (1 : 1400). These two solutions must be kept separate and mixed and filtered only as used, or a precipitate forms and obscures the platelets. In order to get an even distribution of platelets it is well to fill the chamber at once after mixing blood and fluid in the pipet.

I found that waiting an appreciable length of time and shaking as for red blood-corpuscles and white blood-corpuscles is not satisfactory. Wright[17] demonstrated several years ago that platelets tend to adhere to any foreign body and form clumps. This perhaps explains the reduced counts after shaking the pipet. Shaking also tends to form larger and denser clumps, which makes the count very inaccurate. There are three main requisites for reliable platelet counts: namely, the red corpuscles must be laked, the protoplasm of the leukocytes well stained, and the platelets evenly distributed.[4]

After the counting chamber has been filled, it may stand for hours before making the count. It must surely stand ten minutes to allow the platelets thoroughly to settle. The cresyl-blue solution will keep indefinitely on ice, which prevents growth of yeasts. Potassium cyanid should be made up fresh at least every ten days. It must be made of pure potassium cyanid not undergoing degeneration.

Duke found platelet counts fairly constant in normal persons, but fluctuating to extremes in pathologic conditions. By various experimental devices he showed that the platelet count fluctuated in exact proportion to the degree of toxicity. He found that the injection of diphtheria toxin in small doses raised the count, and that the same toxin in lethal or nearly lethal doses decreased the count rapidly. He concluded from his experiments that when increased counts were associated with pathologic conditions, the case was usually mild. In other words, the toxins act as irritants or poisons according to the size of dosage. Duke[6] bore out his deductions in man; his average counts of patients in febrile condition was 114,000 per c.mm.—the convalescent counts going as high as 750,000 per c.mm.

SUMMARY

1. The technic of the various laboratory methods used is described.

2. There was a marked calcium deficiency in jaundice cases of several weeks' duration. Platelets were present in normal numbers.

3. The blood of hemorrhagic purpuras was deficient in platelets. There was no retraction of the clot. Estimation of platelets was of value in differentiating between hemorrhagic purpuras and hemophilias.

4. The coagulation time of epileptic blood was within normal limits.

5. Prothrombin was slightly diminished in pernicious anemia.

6. There was a tendency in myelocytic leukemias for prothrombin time to be prolonged beyond the normal limits of from six to fourteen minutes, although the coagulation time was within normal limits.

7. There was a characteristic delay in coagulation in the blood of hemophiliac cases. There was also a deficiency in prothrombin. Platelets were present in normal numbers, and have normal retractile powers. There was apparently no deficiency in calcium.

8. One patient of special note among the hemophilias had an extremely long coagulation time, though his prothrombin time was within normal limits. His mother had a normal coagulation time, but a markedly delayed prothrombin time.

REFERENCES

1. Addis, T.: The pathogenesis of hereditary hæmophilia. Jour. Path. and Bacter., 1911, xv, 427–452.
2. Cohen, M. S.: The coagulation-time of the blood as affected by various conditions. Arch. Int. Med., 1911, viii, 684–716.
3. Drinker, C. K., and Hurwitz, S. H.: The factors of coagulation in primary pernicious anemia. Arch. Int. Med., 1915, xv, 733–745.
4. Duke, W. W.: The rate of regeneration of blood platelets. Jour. Exper. Med., 1911, xiv, 265–273.
5. Duke, W. W.: The pathogenesis of purpura hæmorrhagica with especial reference to the part played by blood-platelets. Arch. Int. Med., 1912, x, 445–469.
6. Duke, W. W.: Causes of variation in the platelet count; experimental results showing the effect of diphtheria toxin, benzol and tuberculin on the platelet count in rabbits. Arch. Int. Med., 1913, xi, 100–120.
7. Howell, W. H.: The rôle of antithrombin and thromboplastin (thromboplastic substance) in the coagulation of blood. Am. Jour. Physiol., 1911, xxix, 187–209.
8. Howell, W. H.: The condition of the blood in hemophilia, thrombosis, and purpura. Arch. Int. Med., 1914, xiii, 76–95.
9. Hurwitz, S. H., and Lucas, W. P.: A study of the blood in hemophilia. Arch. Int. Med., 1916, xvii, 543–569.
10. Lee, R. J., and White, P. D.: A clinical study of the coagulation-time of blood. Am. Jour. Med. Sc., 1913, cxlv, 495–503.
11. Lee, R. J., and Vincent, B.: The relation of calcium to the delayed coagulation of blood in obstructive jaundice. Arch. Int. Med., 1915, xvi, 59–66.
12. Minot, G. R.: The effect of temperature upon the clotting time (Prothrombin-time) of oxalated plasma with calcium. Jour. Med. Res., 1915–16, xxxiii, 503–506.
13. Minot, G. R., and Lee, R. J.: The blood platelets in hemophilia. Arch. Int. Med., 1916, xviii, 474–495.
14. Thorn, D. A.: Coagulation-time of the blood in epileptics. Ill. Med. Jour., 1914, xxvi, 382–383.
15. Wright, A. E.: On a method of determining the condition of blood coagulability for clinical and experimental purposes, and on the effect of the administration of calcium salts in hæmophilia and actual or threatened hæmorrhage. Brit. Med. Jour., 1893, ii, 223–225.
16. Wright, J. H., and Kinnicutt, R.: A new method of counting the blood-platelets for clinical purposes, and some of the results obtained with it. Jour. Am. Med. Assn., 1911, lvi, 1457–1459.
17. Wright, J. H.: The histogenesis of the blood platelets. Jour. Morphol., 1910, xxi, 263–278.

THE ESTIMATION OF UROBILIN AND UROBILIN-
OGEN IN THE DUODENAL CONTENTS*

H. Z. GIFFIN, A. H. SANFORD, AND T. L. SZLAPKA

In a study of diseases associated with evidence of increased blood destruction it is desirable to attempt to estimate the activity of hemolysis, and to compare this with the probable capacity for blood regeneration. Many workers have used as an index of blood destruction the changes that occur in the contents of the bile, namely, the amount of bile-pigment excreted and especially the amount of urobilinogen and urobilin. Eppinger estimated the amount of urobilinogen and urobilin in the stools by means of the Charnas spectrophotometric method and stimulated interest in this manner of estimating blood destruction, particularly in pernicious anemia and hemolytic icterus. In this country a more simple procedure for making rough quantitative estimates of these substances has been devised by Wilbur and Addis. Robertson, making use of the method, has reported findings in every way comparable to those of Eppinger.

The theories advanced with regard to the fate of hemoglobin after hemolysis are not well substantiated. Recent investigations by Whipple and Hooper are especially important. Their experiments involved a great deal of careful study over a considerable period of time, and, of necessity, only on dogs. Their conclusions are in some respects iconoclastic. If further work substantiates their findings, it may be necessary to change our conception of the factors concerned in the formation of bile-pigment. These authors conclude, especially from their results regarding the influence of diet on bile-pigment production, that the disintegration of red blood-cells is not the important factor in the production of bile-pigments. They have made estimations chiefly of the amount of bilirubin. It will be interesting to learn of their results with respect to urobilin and urobilinogen, for in the clinical studies on

the hemolytic anemias there is now considerable evidence from many observers that the amounts of these substances excreted are definitely increased. This increase, it is true, may be the result of impaired organ function as well as of blood destruction. The quantity of bilirubin does not, however, run constantly parallel to the quantity of urobilin and urobilinogen in pathologic conditions.

In our own studies we have made use of the modifications of the Wilbur and Addis methods, recently devised and reported by Schneider. The essential advance in technic is the application of the observations, not to stool extracts, but to the contents of the duodenum as collected by means of a Rehfuss tube. In this liquid an amount of the biliary pigments and their derivatives sufficient for quantitative determinations is readily obtained in a short time. While an estimation of the amounts of these pigments in the duodenal contents at a given time cannot be regarded as an index of the total amount excreted in twenty-four hours, objections are also advanced with respect to the values obtained in the twenty-four-hour stool, in which some proportion of the substances may be destroyed or changed in character. The values obtained by Schneider's method have been so definitely in accord with the clinical manifestations that there is little doubt of the existence of a relationship which it is to be hoped may be made clearer by further study. These values are also in accord with the results obtained from estimations on the stool. The technic we have used, which in all of its essentials is that described by Schneider, is presented in detail, in order that it may be readily understood and easily followed. We wish to express our indebtedness to the originator of this method for his personal interest in our work.

THE METHOD OF OBTAINING THE DUODENAL CONTENTS*

The tube and the metal capsule employed are similar to those of the Einhorn duodenal tube, but experience has led to the use of a somewhat stiffer tube and a capsule which, though similar in shape, is slightly larger and heavier, weighing 6.4 gm. This model of capsule was recommended by Schneider. However, an ordinary Einhorn or a Rehfuss bucket may be used. For convenience in observing the contents of the tube a piece of glass tubing is inserted at its end.

In the preparation for the examination the patient is instructed to partake of no food for at least twelve hours, except perhaps a little tea

* Described by Szlapka.

or coffee without cream, and to take frequent sips of warm water up to the time of the examination.   The nature and purpose of the test are also explained, as the patient's confidence and coöperation aid in the passage of the tube.

The passage of the duodenal tube is a simple procedure.   The metal capsule is placed on the back of the tongue and the patient is directed to swallow hard several times in rapid succession.   There is usually some difficulty as the capsule reaches the level of the cricoid but this is over-come by deep breathing.   After the capsule has passed this irritable zone, peristalsis carries it along without further discomfort to the patient and largely beyond his control.   He merely swallows from time to time, taking a few sips of warm water and the capsule finally reaches the stomach and comes to rest at about 60 cm. from the incisor teeth.

The patient is now made to lie on his right side, with the hips elevated eight or ten inches.   The pyloric end of the stomach thus becomes more dependent, and gravity, aided by gastric peristalsis, causes the capsule to pass through into position in the duodenum—some 70 cm. from the incisors.   In our experience this is accomplished in from fifteen minutes to an hour, usually in about forty-five minutes.   At no time is it neces-sary to push the tube on its way.   Pushing only tends to coil it up in the stomach and may even frustrate its passage into the duodenum.

With the patient on his side, the end of the tube is allowed to hang well over the edge of the table.   Gastric contents siphon out first, the siphon being started by the injection of a few cubic centimeters of warm water.   As the capsule moves through the pylorus into the duodenum, the fluid recovered becomes yellowish and finally a clear bile is obtained. It may vary in color from light yellow to chocolate brown.   Pure duodenal fluid is faintly alkaline, clear, of quite uniform color and viscid;   the foam is golden.   The liquid must be alkaline.   Its mere appearance is not a safe guide as to its identity, although with experi-ence one may come to recognize it readily.   The character of the fluid collected must be observed closely, as from time to time the pylorus permits the passage of gastric contents into the duodenum.   This impure liquid may be detected by its change in color and its dull, cloudy, opalescent appearance, diminished viscidity, more rapid flow, and change in reaction to litmus or Congo red.   It should, of course, be discarded.

Should the flow of bile become interrupted an unusual length of time, the injection of a little warm water into the tube or the taking of

deep breaths by the patient will help to reëstablish it. The application of suction is neither necessary nor advisable.

It is our custom to collect the duodenal contents in a small, amber-colored bottle, as air and light cause the rapid transformation of the urobilinogen into urobilin; 20 c.c. of liquid are necessary for the test, which should be made immediately.

LABORATORY TECHNIC*

The duodenal contents is poured into a graduated cylinder as soon as it is brought to the laboratory, and its gross appearance noted. Normally it is a light straw-colored, viscid fluid, and this is reported as normal yellow (N). The color may vary to dark yellow, brown, and chocolate. The dark-colored fluids always yield much bilirubin, but the color of the duodenal contents does not always indicate the amount of urobilinogen or urobilin present, as these substances are sometimes demonstrated in considerable amounts in normal yellow fluids. Occasionally, however, in cases other than pernicious anemia or hemolytic icterus, a colorless, watery secretion with no biliary pigments or derivatives is collected.

When 20 c.c. or more of clear duodenal contents is collected, it is divided into two 10 c.c. portions in 25 c.c. graduates. To one 10 c.c. portion is added an equal amount—10 c.c.—of a saturated alcoholic solution of zinc acetate (Schlesinger's solution).† The mouth of the graduate is closed by the thumb and the contents thoroughly mixed by vigorous shaking for about one minute. The mixture is then filtered through a single layer of coarse filter-paper, the filtrate being collected in another clean, dry graduate. When exactly 10 c.c. of filtrate is obtained, it is used for testing for urobilin and urobilinogen. To this mixture, which consists of 5 c.c. of duodenal contents and 5 c.c. of Schlesinger's solution, is added exactly 1 c.c. of Ehrlich's aldehyd reagent,‡ measured with a 1 c.c. pipet. The color of the fluid is usually significant when viewed by transmitted and reflected light. If urobilinogen is present in considerable amount, especially if it predominates, the fluid, on the addition of Ehrlich's reagent, becomes a cherry-red, varying in intensity with the amount of chromogen present. When there is a preponderance of urobilin, the color by transmitted light is

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* Described by Sanford.

† Ethyl alcohol, 500 c.c.; zinc acetate, quantity sufficient for saturation.

‡ Paradimethylaminobenzaldehyd, 4 gm.; hydrochloric acid, 30 c.c.; distilled water, 30 c.c.

yellow or brown, and by reflected light a green fluorescence, characteristic of mixtures of urobilin with zinc salts, is noted.   The graduate is now set in the dark for fifteen minutes before it is examined spectroscopically.   This length of time seems necessary to sufficiently sharpen the absorption-bands of the spectrum, while if the mixture stands for longer intervals of time, some of the mother substance, urobilinogen, may become converted into urobilin.

While waiting before making the spectroscopic examination the second 10 c.c. portion is tested for bilirubin.   To the duodenal contents in the second 25 c.c. graduate is added exactly 10 c.c. of 10 per cent aqueous solution of calcium chlorid, made slightly alkaline to litmus with normal sodium hydrate solution.   The mixture is thoroughly shaken and then poured into two 15 c.c. centrifuge tubes—10 c.c. in each.   It is then rapidly centrifugalized for a few minutes to collect the precipitate into a compact mass.   The supernatant fluid is decanted, and the residue washed out of the tubes with a few cubic centimeters of acid alcohol* into a porcelain evaporating dish.   In all, about 20 c.c. of acid alcohol is used to dissolve the precipitate.   The alcohol mixture is carefully heated on a copper warming stage and allowed to boil vigorously.   The color, which may be brick red, soon changes to green if there is much bilirubin present.   The mixture is concentrated so that its volume just reaches the "U" in an Esbach albuminometer. Alcohol is added to the mark "R."   The color of the fluid by transmitted light is then compared with three standard tubes marked *, **, ***, according to the shade of emerald green as viewed by transmitted light.   The standard tubes are prepared arbitrarily from specimens containing appreciable amounts, moderately large amounts, and excessive amounts of bilirubin.   These alcoholic solutions may be kept indefinitely without change of color, though it may be advisable to place the tube in the dark when it is not in use.

The first mixture is now examined spectroscopically for urobilinogen and urobilin.   The spectroscope we use is of the simple students' type, having a collimator with a slit adjustable by a thumb-screw, a scale tube, and a draw-tube type of telescope.   The light we use is a 250-watt tungsten electric lamp, mounted on a stand with a green shade reflector. This is adjusted so that when the collimator of the spectroscope is placed about eight inches from the globe, a brilliant spectrum is produced. The glare of the light is kept from the eyes by the shade of the lamp,

* Hydrochloric acid, 5 c.c.; alcohol, 20 c.c.

and by a shie'd of black cardboard perforated so that it may be slipped on the collimator tube. For observing the absorption-bands Schneider uses a 50 c.c. graduated cylinder. Our own observations were made in this manner up to October 1, 1916; since that time we have used a spectrum cell with parallel sides, and of such dimensions that the distance traversed by the rays of light in passing through the fluid is exactly one centimeter. Schneider opens the slit of the collimator eight half-turns or four full turns of the adjusting screw when using a cylinder for examining the solution. We have found this slit too wide with the standard spectrum cell, and have accordingly used a slit of just half the width. Thus, to adjust the collimator, we completely close the slit and then open it by four half-turns or two complete turns of the adjusting screw. This gives apparently about the same degree of absorption with the standard cell as is obtained with the cylinder when the slit is twice as wide, so that in this way all readings are made to conform to Schneider's standard.

The presence of urobilin is marked by a broad band in the blue end of the spectrum. The violet rays are completely absorbed, and if there is much urobilin present, the entire blue portion and nearly all of the green may be obliterated. Urobilinogen absorbs a narrow portion of the spectrum in the yellow at the edge of the green, and if present in large amounts, the band may be broad enough to obliterate the entire yellow portion of the spectrum. It is located by its proximity to the "D" Fraunhofer line while urobilin extends from between the "B" and "F" lines to the violet end of the visible spectrum.

The method used by Schneider to estimate the quantity of the absorbing substance is that suggested by Wilbur and Addis. The solution is diluted carefully with alcohol until the absorption-bands disappear. The urobilinogen and urobilin differ in their intensity; consequently the disappearance of the absorption-bands will occur with different dilutions, although at times the same dilution causes the clearing of the spectrum in both regions. The end point is determined when the absorption-band disappears, but can be made out faintly when the slit is narrowed to just half of its former opening; that is, when the cylinder method is used, the adjusting screw is turned four half-turns. With the standard spectrum cell the end point is determined by causing the reappearance of absorption-bands with two half-turns.

The amount of urobilin and urobilinogen is estimated according to the Wilbur and Addis method for 1000 c.c. by multiplying the number

of dilutions by 200.   This factor is used since 5 c.c. of duodenal contents is represented in 10 c.c. of filtrate obtained from the mixture with the Schlesinger solution.   The number of units of urobilinogen and urobilin are added together and the total number of units reported, for example, urobilinogen (three dilutions) 3 × 200 = 600 units; urobilin (four dilutions) 4 × 200 = 800 units; total, 1400 units.

<p style="text-align:center">CLINICAL OBSERVATIONS*</p>

A total of 119 tests have been made in 89 cases.   The results will be considered in three groups:

1. Results obtained in a series of miscellaneous cases of which there were 22 and 22 tests.

2. The findings in hemolytic jaundice, 6 cases, 12 tests.

3. The findings in pernicious anemia, 61 cases, 85 tests.

The study includes the tests made in all cases up to November 15, 1916, with the exception of 9 in which the diagnoses were so obscure as to render the results positively and negatively valueless.   Brief protocols of the 22 cases in the miscellaneous group are presented.

<p style="text-align:center">1. MISCELLANEOUS CASES</p>

Anemia from Hemorrhage

CASE 1 (157200).—Woman, aged fifty years.   Uterine myomas. Hysterectomy.   Spleen normal in size but hard;   liver congested. Hemoglobin, 30 per cent; red blood-cells, 3,470,000.

Duodenal contents: Color, yellow.   Urobilin, 200 units; urobilinogen, trace; total, 200 + units.

CASE 2 (164791).—Woman, aged forty-one years.   Hysterectomy. Appendectomy.   Spleen twice normal size;   liver slightly enlarged. Hemoglobin, 35 per cent; red blood-cells, 3,190,000.

Duodenal contents: Color, yellow.   Urobilin, 200; urobilinogen, 0; total, 200.

CASE 3 (156514).—Woman, aged forty-seven years.   Cervical polyp. Melancholia of climacteric.   Liver normal;   spleen normal.   Hemoglobin, 50 per cent; red blood-cells, 3,600,000.

Duodenal contents: Urobilin, 200; urobilinogen, 0; total, 200.

CASE 4 (150583).—Man, aged fifty-nine years.   Bleeding hemorrhoids.   Liver just palpable; spleen normal.   Hemoglobin, 30 per cent; red blood-cells, 3,340,000.

Duodenal contents: Color, yellow.   Urobilin, trace; urobilinogen, trace; total, less than 200.

<p style="text-align:center">* Made by Giffin.</p>

'17—30

CASE 5 (172166).—Woman, aged twenty-five years. Slight menor-rhagia. Liver normal; spleen normal. Hemoglobin, 60 per cent; red blood-cells, 4,460,000.

Duodenal contents: Color, yellow. Urobilin, 500; urobilinogen, 0; total, 500.

Chronic Arthritis

CASE 6 (85456).—Man, aged fifty-one years. Mild arthritis and neuralgia. Liver normal; spleen just palpable. Hemoglobin, 72 per cent; red blood-cells, 4,620,000.

Duodenal contents: Color, yellow. Bilirubin, trace; urobilin, 800; urobilinogen, 0; total, 800.

CASE 7 (131120).—Man, aged fifty years. Mild chronic arthritis; dental abscesses; chronic tonsillitis. Liver normal; spleen normal. Possibility of pernicious anemia. Hemoglobin, 38 per cent; red blood-cells, 1,700,000; white blood-cells, 12,200; color index, 1.1. (One year ago hemoglobin, 57 per cent; red blood-cells, 4,080,000).

Duodenal contents: Urobilin, 600; urobilinogen, 600; total, 1200.

Dental Abscesses. Anemia of Secondary Type

CASE 8 (162929).—Woman, aged thirty-two years. Liver normal; spleen just palpable. Hemoglobin, 52 per cent; red blood-cells, 4,520,000.

Duodenal contents: Color, yellow. Bilirubin, trace. Urobilin, 600; urobilinogen, 0; total, 600.

Cholelithiasis

CASE 9 (151433).—Woman, aged fifty-seven years. Gallstones. Slight possibility of pernicious anemia. Cholecystectomy. Liver normal; spleen normal. Hemoglobin, 49 per cent; red blood-cells, 2,360,-000; color index, 1.

Duodenal contents: Color, yellow. Urobilin, 600; urobilinogen, 0; total, 600.

Syphilis

CASE 10 (153153).—Woman, aged thirty-two years. Syphilis of the liver and spleen. Splenectomy April 29, 1916; spleen, 760 grams. Liver very large, with gummas and contractures. Hemoglobin, 49 per cent; red blood-cells, 3,430,000.

Duodenal contents: Color, yellow. Urobilin, 1000; urobilinogen, trace; total, 1000+.

CASE 11 (151226).—Woman, aged thirty-four years. Probable luetic anemia. Some evidence of nephritis. Absence of history of pernicious anemia. Liver normal; spleen normal. Hemoglobin, 45 per cent; red blood-cells, 3,330,000; color index, .6.

Duodenal contents: Color, yellow. Bilirubin, trace. Urobilin, 800; urobilinogen, 0; total, 800.

Carcinoma

CASE 12 (169462).—Man, aged forty-five years. Carcinoma of stomach. Roentgen findings of extensive carcinoma. Wassermann negative. Hemoglobin, 29 per cent; red blood-cells, 3,190,000.

Duodenal contents: Color, yellow. Urobilin, 400; urobilinogen, trace; total, 400+.

Tuberculosis

CASE 13 (162671).—Woman, aged thirty years. Tuberculous salpingitis. Tuberculous peritonitis found at operation elsewhere. Moderate splenomegaly. Hemoglobin, 35 per cent; red blood-cells, 4,410,000.

Duodenal contents: Color, brown. Bilirubin ++; urobilin, 400; urobilinogen, 600; total, 1000.

Chronic Septic Splenomegaly

CASE 14 (154572).—Woman, aged thirty-one years. Chronic septic splenomegaly. History of scarlet fever, frequent sore throat, and "grippe." Attacks of left upper abdominal pain two years. Cesarean section fifteen months previously. Two weeks afterward excruciating upper abdominal pain. Exploration elsewhere, large spleen found, but nothing done. History suggestive of abdominal thrombophlebitis. Splenectomy April 12, 1916; spleen, 365 grams. Multiple infarcts. Hemoglobin, 50 per cent; red blood-cells, 4,600,000; white blood-cells, 10,400.

Duodenal contents: Color, yellow. Urobilin, 400; urobilinogen, 0; total, 400.

Splenic Anemia

CASE 15 (158085).—Man, aged twenty-nine years. Splenic anemia. History of severe hemorrhages. Melena. Splenectomy; spleen, 780 (?) grams; liver moderately enlarged. Hemoglobin, 45 per cent; red blood-cells, 3,330,000; white blood-cells, 3600.

Duodenal contents before splenectomy: Color, yellow. Bilirubin, trace. Urobilin, 1000; urobilinogen, 200; total, 1200.

Portal Atrophic Cirrhosis of Liver

CASE 16 (148570).—Man, aged sixty-two years. Portal atrophic cirrhosis of the liver. History of alcoholism. Ascites. Liver, 720 grams; spleen, 450 grams. Hemoglobin, 70 per cent; red blood-cells, 3,530,000.

Duodenal contents: Color, yellow. Bilirubin, ++; urobilin, 1000; urobilinogen, trace; total, 1000+.

Polycythemia

CASE 17 (174186).—Man, aged fifty-one years. Polycythemia. Cyanosis. Liver moderately enlarged; spleen moderately enlarged.

Diabetes, ten-year history. Nine months previously red blood-cell count elsewhere, 9,500,000. X-ray treatment with improvement. At present, hemoglobin, 93 per cent; red blood-cells, 5,320,000. Coagulation time, ten minutes (Boggs). Bleeding time, five minutes.

Duodenal contents: Color, brown. Bilirubin, +++; urobilin, 500; urobilinogen, 500; total, 1000.

Myelogenous Leukemia

CASE 18 (157746).—Man, aged thirty-two years. Spleen enormously enlarged; liver slightly enlarged. Slight degree of jaundice. Duration of history one and one-half years. Splenomegaly one year. Hemoglobin, 45 per cent; red blood-cells, 3,120,000; white blood-cells, 496,000; myelocytes, 43.7 per cent.

Duodenal contents: Color, yellow. Urobilin, trace; urobilinogen, trace; total, less than 200.

CASE 19 (158647).—Man, aged fifty-two years. Spleen enormously enlarged. Liver normal. Jaundice questionable. Length of history one year. Splenomegaly six months. Hemoglobin, 55 per cent; red blood-cells, 3,450,000; white blood-cells, 307,000; myelocytes, 29.7 per cent.

Duodenal contents: Color, yellow. Bilirubin, trace; urobilin, 2000; urobilinogen, 540; total, 2540.

CASE 20 (159989).—Man, aged thirty-nine years. Spleen moderately enlarged; liver normal. Jaundice(?) Length of history, twenty-two months. Splenomegaly ten months. Hemoglobin, 53 per cent; red blood-cells, 3,210,000; white blood-cells, 341,000; myelocytes, 29 per cent.

Duodenal contents: Color, yellow. Urobilin, 800; urobilinogen, 0; total, 800.

CASE 21 (173747).—Man, aged thirty-nine years. Spleen enormously enlarged; liver moderately enlarged. Slight jaundice. Splenomegaly two years. Hemoglobin, 42 per cent; red blood-cells, 2,180,000; white blood-cells, 8200; myelocytes, 15.7 per cent.

Duodenal contents: Color, brown. Bilirubin, +++; urobilin, 900; urobilinogen, 200; total, 1100.

Combined Sclerosis

CASE 22 (154069).—Man, aged thirty-eight years. Marked ataxia; duration, six months. Neurologic examination showed findings of advanced combined sclerosis. Wassermann tests negative. Hemoglobin, 54 per cent; red blood-cells, 3,720,000; color index, .7. The existence of pernicious anemia is highly probable.

Duodenal contents: Color, brown. Bilirubin, +++; urobilin, 5500; urobilinogen, 2000; total, 7500.

A summary of the values is given in Table 1.

TABLE 1.—MISCELLANEOUS CASES: SUMMARY OF VALUES

	· CASES	UROBILIN	UROBILINOGEN
Anemia from hemorrhage (averages)	5	275+	0 or trace
Chronic arthritis (averages)	2	700	300
Dental abscesses	1	600	0
Cholelithiasis	1	600	0
Syphilis (averages)	2	900	0 or trace
Carcinoma	1	400	Trace
Tuberculous salpingitis	1	400	600
Chronic septic splenomegaly	1	400	0
Splenic anemia	1	1000	200
Portal atrophic cirrhosis	1	1000	Trace
Polycythemia	1	500	500
Myelogenous leukemia (averages)	4	925+	185
Combined sclerosis (pernicious anemia?)	1	5500	2000

All these patients save three suffered from a moderate or severe anemia. The patient with polycythemia had a hemoglobin of 93 per cent and a red-cell count of 5,320,000 at the time of examination; the value for urobilin was 500 units and that for urobilinogen 500 units. The patient with portal cirrhosis had a hemoglobin of 70 per cent and a red-cell count of 3,530,000; the urobilin was 1000 units and urobilinogen a trace. One of the patients with chronic infectious arthritis had a hemoglobin of 72 per cent and a red-cell count of 4,620,000; the urobilin was 800 units and urobilinogen zero. These three determinations are unaffected by anemia. They all show total values of approximately 1000 units. It has been concluded by other observers that total values of 1000 units or less are normal.

The values in cases of anemia from hemorrhage were especially low—possibly indicating an actual decrease of blood destruction below normal. In anemias of infectious origin, in syphilis, in carcinoma, and in cirrhosis of the liver the total values for urobilin and urobilinogen were 1000 units or less. Three of four patients with myelogenous leukemia gave low determinations; in one, however, the total was 2540 units.

The group as a whole demonstrates consistently low values for the purely secondary types of anemia, irrespective of the severity of the anemia. Patients with simple anemia from hemorrhage present the lowest values of the series.

2. HEMOLYTIC JAUNDICE

Twelve determinations of the pigments in the duodenal contents have been made in six patients with hemolytic jaundice. Brief protocols of these cases follow:

CASE 1 (112836).—Woman, aged forty-nine years. Acquired type of hemolytic jaundice, with the blood-picture of a primary anemia. Increased fragility of erythrocytes. Gallstones and a large slightly cirrhotic liver were found at operation. Weight of spleen, 910 grams. Patient returned during relapse one year and eight and one-half months after splenectomy. The liver was then very large. Hemoglobin, 45 per cent; red blood-cells, 3,260,000; white blood-cells, 3400; normoblasts, 152 in 300 cells. Duodenal test, one year eight and one-half months after splenectomy: Color, brown. Bilirubin, +++; urobilin, 3000; urobilinogen, 1000; total, 4000. The patient improved markedly after two transfusions, but a subsequent estimation of the pigments was not made.

CASE 2 (153245).—Woman, aged thirty-eight years. Severe case of congenital type with enlarged liver and gallstones. Increased fragility of erythrocytes. Weight of spleen, 1700 grams. Hemoglobin, 47 per cent; red blood-cells, 2,840,000; white blood-cells, 9800; no normoblasts.
Duodenal test one day before splenectomy: Color, yellow. Bilirubin, +++; urobilin, 4600; urobilinogen, 1000; total, 5600. Thirty-eight days after splenectomy: Color, yellow. Bilirubin, trace; urobilin, 1400; urobilinogen, 1800; total, 3200. The hemoglobin at the time of the latter test was 70 per cent; red cells, 4,960,000; no normoblasts.

CASE 3 (148209).—Man, aged twenty years. Mild case of congenital type. Increased fragility of erythrocytes. At operation liver showed evidence of early cirrhosis. Weight of spleen, 300 grams. Hemoglobin, 70 per cent; red blood-cells, 4,920,000.
Duodenal test forty-seven days before splenectomy: Color, yellow. Bilirubin, trace; urobilin, 1400; urobilinogen, 1000; total, 2400. Fourteen days before splenectomy: Color, yellow. Bilirubin, trace; urobilin, 2000; urobilinogen, 1200; total, 3200. Thirteen days after splenectomy: Color, yellow. Urobilin, 800; urobilinogen, 1000; total, 1800. One hundred and forty days after operation: Color, yellow. Urobilin, trace; urobilinogen, 400; total, 400+.

CASE 4 (161538).—Woman, aged twenty-seven years. Moderately severe case of congenital type. Increased fragility of erythrocytes. Liver probably normal. Gallstones present. Weight of spleen, 560 grams. Hemoglobin, 64 per cent; red blood-cells, 3,860,000.
Duodenal test three days before splenectomy: Color, yellow. Uro-

bilin, 500; urobilinogen, 500; total, 1000. Twenty-three days after splenectomy: Color, light brown. Bilirubin, trace; urobilin, 400; urobilinogen, 0; total, 400. At the time of the latter test the hemoglobin was 70 per cent, the red blood-cells 4,680,000.

CASE 5 (162670).—Man, aged thirty-one years. Moderately severe case, probably of congenital type. Increased fragility of erythrocytes. Liver normal. Gallstones present. Spleen weighed 1250 grams. Hemoglobin, 67 per cent; red blood-cells, 3,650,000. Considerable deformity of red cells.

Duodenal test four days before splenectomy: Color, brown. Bilirubin, +++; urobilin, 1400; urobilinogen, 1800; total, 3200. Twenty-one days after splenectomy: Color, brown. Bilirubin, ++; urobilin, 1000; urobilinogen, 200; total, 1200. The hemoglobin at the time of the latter test was 80 per cent; red blood-cells 4,022,000.

CASE 6 (153653).—Man, aged twenty-three years. Mild case with some evidence that a familial factor was present. Increased fragility of erythrocytes. Non-operative. Spleen moderately enlarged. Hemoglobin, 60 per cent; red blood-cells, 3,900,000; white blood-cells, 5800; no normoblasts.

Duodenal test: Color, dark yellow. Bilirubin, +; urobilin, 3000; urobilinogen, trace; total, 3000+. (The low urobilinogen may have been due to delay in making the estimation.)

The values for urobilin and urobilinogen in the duodenal contents are very markedly increased in cases of hemolytic jaundice. A few reported cases have shown even higher values than those we have demonstrated. High values are found even when a moderate degree of anemia is present. In Case 3, at the time of the first two tests, the anemia was not severe; however, abnormally large amounts of pigment were obtained. Severe grades of anemia are associated with very high values; in Case 2, with a red cell count of 2,840,000, the total values were 5600 units. If these values are a reasonably accurate index of hemolysis, blood destruction in hemolytic jaundice is probably much increased at a time when blood production is not seriously affected. This is in contrast to our experience with pernicious anemia, in which the evidence of bone-marrow insufficiency is usually marked and the evidence of blood destruction extremely variable. Patients with pernicious anemia, who show high values for urobilin and urobilinogen at a time when the blood count is low, frequently show very low values when the blood count has risen to the level of a moderate anemia. Patients with hemolytic jaundice, on the other hand, may show high values, with only a slight anemia. In two patients with very high values the blood-picture

simulated that of pernicious anemia. An excessive degree of blood destruction probably exhausted the bone-marrow.

In four of these patients tested before and after operation there was an appreciable reduction in the values for bile-pigments following splenectomy. In two of them a decided decrease in the amount of urobilinogen was revealed. In Case 3 a former operation for cholecystitis had not reduced the values to normal. The preoperative values of these four patients averaged 2050 units for urobilin and 1100 units for urobilinogen, a total of 3150 units. The average postoperative values at periods varying from thirteen days to four months after splenectomy were 800 units for urobilin and 625 units for urobilinogen, a total of 1425 (Table 2).

TABLE 2.—ESTIMATION OF PIGMENTS IN THE DUODENAL CONTENTS: HEMOLYTIC JAUNDICE

Case No.	Time Before and After Splenectomy	Color	Bilirubin (Units)	Urobilin (Units)	Urobilin-ogen (Units)	Total (Units)
1 (112836)	1 year 8½ months after	Brown	+++	3000	1000	4000
2 (153245)	1 day before	..	+++	4600	1000	5600
	38 days after	Yellow	Trace	1400	1800	3200
3 (148209)	47 days before	Yellow	Trace	1400	1000	2400
	14 days before	Yellow	Trace	2000	1200	3200
	13 days after	Yellow	0	800	1000	1800
	140 days after	Yellow	0	Trace	400	400+
4 (161538)	3 days before	Yellow	..	500	500	1000
	23 days after	Light brown	Trace	400	0	400
5 (162670)	4 days before	Brown	+++	1400	1800	3200
	21 days after	Brown	++	1000	200	1200
6 (153653)	Non-operative	Dark yellow	+	3000	Trace	3000+
Average values before splenectomy 4 cases..				2050	1100	3150
Average values after splenectomy 4 cases...				800	675	1475

3. PERNICIOUS ANEMIA

Eighty-five estimations were made in 61 cases of pernicious anemia. In 6 of the cases the tests were done only after splenectomy, thereby reducing the number of medical and preoperative observations from 61 cases to 55 cases. The average of the readings for urobilin in these 55 cases was 1856.5 units, and that for urobilinogen, 1604.5 units. The average total for urobilin and urobilinogen was, therefore, 3461 units.

This average is approximately four times normal, and remarkably close to the figure obtained by Schneider in his recently reported series.

Nine of the 55 patients showed total values less than 1000; in other words, 84 per cent gave values of 1000 units and over. It is our experience that patients more than fifty-five years of age, and particularly more than sixty years of age, not uncommonly show low values. In these senile types there is frequently evidence of advanced bone-marrow damage, with little active hemolysis. Some of these anemias may, in reality, be osteosclerotic in origin, but this distinction is difficult to make clinically.

It is also our experience that, as the blood improves in pernicious anemia, the duodenal values quickly decline. When the red cells reach 3,500,000, the duodenal values are quite apt to run below 1000 units total. The average in 3 patients with red-cell counts above 3,500,000 cells was 433.3 units for urobilin and 466.6 units for urobilinogen, making a total of 899.9 units. Moreover, a few patients who have had repeated tests during treatment have shown this same rapid decline in values when the anemia became of moderate grade. Hemolytic jaundice, on the other hand, gave high values even when the anemia was slight.

It is, therefore, to be concluded that a certain number of patients with undoubted pernicious anemia do show low total values at certain times. On the other hand, urobilinogen will be present in an appreciable amount. The most noteworthy constant is the presence of an estimable amount of urobilinogen. Urobilinogen was absent in only 1 of the 55 medical and preoperative cases; in 2 others there was a trace; in 52, urobilinogen was present in relatively large amounts; in 24, or nearly one-half of the cases, urobilinogen was present in even larger amounts then urobilin. The presence of large quantities of urobilinogen before splenectomy, and its complete absence in at least 75 per cent of the cases after splenectomy, are very striking findings and may have an important significance.

The highest total values were obtained in patients with red-cell counts between 2.5 and 3.5 million cells. They were slightly lower in patients with erythrocyte counts between 1.5 and 2.5 million cells and considerably lower in patients with erythrocyte counts below 1.5 million cells. The lowest values were obtained in patients with counts over 3.5 million cells, but even in these urobilinogen was present in a distinctly abnormal amount. The most active hemolysis seems to occur in the patients with counts between 2.5 and 3.5 million cells, but this may be due to the fact that patients are only rarely seen at the onset

of a period of active blood destruction. As a group, these latter cases
show evidence of very active hemolysis, and at the same time evidence
of active blood production (Table 3).

TABLE 3.—ESTIMATION OF PIGMENTS IN THE DUODENAL CONTENTS—
VALUES WITH RESPECT TO ERYTHROCYTE COUNT

PERNICIOUS ANEMIA (MEDICAL AND PREOPERATIVE)

	NUMBER OF ESTIMATIONS	AVERAGE UROBILIN (UNITS)	AVERAGE UROBILINOGEN (UNITS)	TOTAL (UNITS)
Erythrocytes 1.5 millions and below	11	1496.3	1472.7	2969.0
Erythrocytes 1.5 to 2.5 millions	32	1864.3	1725.0	3589.3
Erythrocytes 2.5 to 3.5 millions	13	2346.1	1653.8	3999.9
Erythrocytes 3.5 millions and over	3	433.3	466.6	899.9

HEMOLYTIC JAUNDICE (MEDICAL AND PREOPERATIVE)

Erythrocytes 3.5 millions and over	4	1650.0	850.0	2500.00

Age.—The average totals for patients under fifty-five years of age
showed very little variation by decades. Over the age of fifty-five
there was a decided drop both in urobilin and urobilinogen. Between
the ages of fifty-six and sixty years the totals average 2644.2; over the
age of sixty they average 1600, while under fifty-five the average totals
for decades vary between 3325 and 4238 (Table 4).

TABLE 4.—ESTIMATION OF PIGMENTS IN THE DUODENAL CONTENTS:
VALUES WITH RESPECT TO AGE

PERNICIOUS ANEMIA (MEDICAL AND PREOPERATIVE)

AGE OF PATIENT	NUMBER CASES	AVERAGE UROBILIN (UNITS)	AVERAGE UROBILINOGEN (UNITS)	TOTAL (UNITS)
30 years and under	3	2266.6	1833.3	4099.9
31–40	10	1955.0	1370.0	3325.0
41–50	12	2075.0	1691.6	3766.6
51–55	16	2200.6	2037.5	4238.1
56–60	9	1372.0	1272.2	2644.2
Over 60 years	5	660.0	940.0	1600.0

Size of spleen.—High values were obtained both in patients with
large spleens and in those with small spleens. Lower values were
obtained in those with spleens of moderate size, that is, weighing from
200 to 500 gm. The highest urobilinogen values were obtained in
patients with spleens of 200 gm. and less. It is impossible to determine
the significance of these findings with respect to the size of the spleen.
The degree of pathologic or of functional damage in the liver may be
the important factor. Patients with small spleens have more con-

stantly shown evidence of advanced pathologic change in the liver (Table 5).

TABLE 5.—ESTIMATION OF PIGMENTS IN THE DUODENAL CONTENTS: VALUES WITH RESPECT TO WEIGHT OF SPLEEN

PERNICIOUS ANEMIA (PREOPERATIVE ESTIMATIONS)

WEIGHT OF SPLEEN	NUMBER CASES	AVERAGE UROBILIN (UNITS)	AVERAGE UROBILIN-OGEN (UNITS)	TOTAL (UNITS)
200 grams and below................	4	3000.0	2000.0	5000.0
200 grams to 500 grams.............	12	2342.5	1487.5	3830.0
Over 500 grams..........	6	3233.3	1433.3	4666.6

VALUES AFTER SPLENECTOMY

A very striking reduction is observed in the values after splenectomy. A total of 19 patients was examined after splenectomy; 13 both before and after operation. The average of the total values for these 13 patients became reduced from 4492.2 to 1134.6 units. Urobilinogen in 10 of the 13 cases was reduced to zero or a trace. Of the entire group of 19 examined after splenectomy, 13 gave values for urobilinogen of zero or a trace. Three showed urobilinogen over 1000 units after splenectomy, but judging from the clinical history these readings probably became reduced later.

Two patients who had high values for urobilinogen following splenectomy, showed no definite improvement in the anemia. The liver was enlarged in each instance, and an exposure of the liver to radium was suggested. The application of 50 mg. of radium over five areas for a total of ten hours was followed by a very marked reduction in the size of the liver, a fall in duodenal values and a prompt improvement in the anemia (Tables 6 and 7).

TABLE 6.—ESTIMATION OF PIGMENTS IN THE DUODENAL CONTENTS: PREOPERATIVE AND POST-OPERATIVE VALUES

	NUMBER CASES	AVERAGE UROBILIN (UNITS)	AVERAGE UROBILIN-OGEN (UNITS)	TOTAL (UNITS)
Pernicious anemia (medical and pre-operative)........................	55	1856.5	1604.5	3461.0
Pernicious anemia (preoperative).......	13	2970.7	1521.5	4492.2
Pernicious anemia (post-operative)	13	815.4	319.2	1134.6
Pernicious anemia (post-operative)	10 of the 13	480.0	0 or trace	480+
Hemolytic jaundice (preoperative)......	4	2050.0	1100.0	3150.0
Hemolytic jaundice (post-operative)....	4	800.0	675.0	1475.0

TABLE 7.—ESTIMATION OF PIGMENTS IN THE DUODENAL CONTENTS
PERNICIOUS ANEMIA (SPLENECTOMY)

Case Number	Date of Splenectomy	Time Before and After Splenectomy	Color	Bilirubin (Units) Before operation	Bilirubin (Units) After operation	Urobilin (Units) Before operation	Urobilin (Units) After operation	Urobilinogen (Units) Before operation	Urobilinogen (Units) After operation	Total (Units) Before operation	Total (Units) After operation	Red Blood-Cells (Millions)	Weight of Spleen (Grams)
1 (153922)	3/10/16	7 days before	Yellow	+++		2000		600		2800		1.96	150
		21 days after			+		1400		0		1400	1.48	
2 (152671)	5/15/16	20 days before	...	...		5000		1000		6000		2.94	508
		13 days before	...	...		6000		4000		10000		4.4	
		21 days after			...		800		0		800	2.34	
3 (154493)	3/25/16	9 days before	Brown	+		5000		2000		5000		1.89	525
		17 days after	Yellow		++		200		0		200	2.53	
4 (153395)	3/29/16	9 days before	Brown	+++		3500		trace		3500+		3.14	450
		24 days after	Yellow		trace		trace		trace		200—	2.8	
5 (154299)	4/8/16	9 days before	Brown	+++		4000		2000		6000		2.73	153
		21 days after	Brown		++		6800		1400		2800	2.16	
		4 months after	Brown		+++		1800		1400		3200	2.96	
6 (157146)	4/20/16	3 days before	Brown	+++		5200		2600		5800		3.25	270
		19 days after	Brown		trace		1400		trace		1400+	2.46	
7 (151021)	5/4/16	5 days before	Yellow	+		5400		4800		10000		1.96	111
		27 days after	Yellow		trace		200		0		200	2.41	
8 (157665)	6/2/16	1 month before	Brown	+		840		760		1600		2.22	410
		14 days before	Yellow			500		600		1100		3.49	
		2 months after	Yellow		+		400		0		400	1.66	
9 (157290)	6/5/16	2 months before	Yellow	+		600		800		1400		5.2	192
		18 days after	Yellow		trace		trace		trace		200—	2.72	
10 (161677)	6/15/16	6 days before	Yellow	+++		400		400		800		3.0	770
		26 days after	Yellow		++		trace		0		200—	3.53	
11 (160970)	6/27/16	11 days before	Brown	+++		800		200		1000		4.58	500
		29 days after	Yellow		trace		trace		0		200—	1.61	
12 (158156)	6/28/16	2 months before	Brown	+++		2500		2000		4500		1.94	500
		7 days before	Brown	+++		600		600		1200		1.8	
		25 days after	Yellow		++		800		1400		2200	3.25	
13 (170115)	10/3/16	2 days before	Brown	+++		8000		2000		10000		2.65	600
		1 month after	Brown		+++		400		1300		2100	3.14	
		2 months after	Yellow		+		600		800		1400			

TRANSFUSIONS

Transfusions did not seem to affect the duodenal values.   However, estimations were not made the first or second day following transfusion, at which time an increase in the amounts of pigments might be expected. Estimations made five and ten days following transfusion gave no unusual values.

BILIRUBIN

An excess of bilirubin was usually present when large amounts of urobilin and urobilinogen were found.   This relationship was by no means constant.   An excess of bilirubin was not infrequently found with low values for urobilin and urobilinogen, and very small amounts of bilirubin were occasionally found with high values.   The amount of bilirubin, therefore, does not run parallel with the values for urobilin and urobilinogen.   These values are probably indicative of some quite different function or impairment of function in pathologic conditions.

SUMMARY

1. With a few slight modifications of technic we have used the method of Schneider in estimating quantitatively the amounts of urobilinogen and urobilin in the duodenal contents obtained by means of an Einhorn tube.   The procedures are simple and can be carried out in any clinical laboratory.   The results are comparable with those obtained by the more complicated and time-consuming methods in which stool-extracts are used for the estimation of these pigments.

2. In a group of 22 miscellaneous cases low values were obtained in patients with anemia from hemorrhage, carcinoma, tuberculous peritonitis, syphilis, portal cirrhosis, chronic infectious arthritis, and gallstones.   They were low in three of four patients with myelocytic leukemia.   The amounts of these pigments were especially low in cases of anemia from hemorrhage.

3. In hemolytic jaundice the values were consistently high, even when severe anemia was not present.   The values fell appreciably after splenectomy, but not as promptly as in pernicious anemia.

4. In pernicious anemia the amounts of urobilin and urobilinogen in the duodenal contents were above normal in 84 per cent of the cases. The amount of urobilinogen was constantly increased when the anemia was severe.   Patients over the age of fifty-five showed lower values than

younger patients. The values presented no definite relationship to the size of the spleen. Following splenectomy there was a very definite decrease in the amounts of urobilin and urobilinogen; the decrease in urobilinogen was especially noticeable.

5. The amounts of bilirubin in the duodenal contents did not run constantly parallel to the amounts of urobilin and urobilinogen.

REFERENCES

1. Eppinger, H.: Zur Pathologie der Milzfunktion. (I Mitteilung.) Berl. klin. Wchn-schr., 1913, 1, 1509–12; 1572–76. (II Mitteilung.) 2409–11.
2. Hooper, C. W., and Whipple, G. H.: Bile pigment metabolism. Am. Jour. Physiol., 1916, xl, 332–48; 349–59; 1917, xlii, 256–263; 264–79; 544–57.
3. Robertson, O. H.: Urobilin in the stool—an index to blood destruction. Arch. Int. Med., 1915, xv, 1072–78.
   Urobilin in the stool as influenced by splenectomy transfusion and salvarsan. Arch. Int. Med., 1915, xvi, 429–36.
4. Schneider, J. P.: The hematopoietic-hemolytic index: a proposed determination help-ful in the differential diagnosis of types of pernicious anemia amenable to cure by splenectomy. Journal-Lancet, 1917, xxxvii, 105–108.
   Further quantitative study of the duodenal blood derived pigments. Arch. Int. Med., 1917, xix, 156–62.
   The splenic pathology of pernicious anemia and allied conditions. Arch. Int. Med., 1916, xvii, 32–41.
5. Wilbur, R. L., and Addis, T.: Urobilin: its clinical significance. Arch. Int. Med., 1914, xiii, 235–86.

SELECTION OF THE DONOR FOR TRANSFUSION*

A. H. SANFORD

For years transfusion has been looked upon as a valuable emergency life-giving measure. Recent simplification in technic has brought it into popular favor, and the benefits of this form of therapy can now be utilized by any physician. The obstacles in the way of transfusion at present are not difficulties in the operation itself, but fears arising from the knowledge that the selection of a donor is a matter of absolute moment, and that the results may be most disastrous if a weak, perhaps dying, patient is suddenly shocked by the introduction within his veins of incompatible blood.

Years ago Landsteiner pointed out the fact that human beings can be classified in groups by studying the action of the serum of one person upon the corpuscles of another. Several years later Moss made the discovery that there were not only three groups, as the former worker had reported, but a fourth group. The interrelation of the Moss agglutination groups is easily understood from the accompanying diagram (Fig. 154).

It is evident that care must be exercised in the selection of the donor. If possible, it is best to have the donor and the patient in the same group. This is not absolutely necessary, however. The rule for the selection of the donor is evolved on common-sense principles. Blood of a donor containing agglutinin for the patient's corpuscles can be transfused with impunity, as it is immediately diluted and diffused in the patient's own blood, doing little, if any damage, to his corpuscles. On the other hand, if a donor's corpuscles are agglutinated by the patient's serum, the transfusion will result in an immediate clumping together of the trans- fused corpuscles. The mass action of a large amount of agglutinating serum on a comparatively small amount of corpuscles produces a reac- tion in the patient similar in all respects to anaphylactic shock. A study of the diagram makes it appear that any donor can be used for

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Group 1 individuals, as they cannot agglutinate corpuscles from any group. On the other hand, Group 4 persons (43 per cent of all) must have donors from their own group, as their serum agglutinates the corpuscles of all other groups. However, a Group 4 donor can be used for any one, as his corpuscles are not agglutinable. Group 2 and Group 3 donors are, of course, absolutely incompatible with each other. Patients of these groups must have donors of their own group or of Group 4.

There are several methods for selecting donors which I shall review briefly before describing in detail a simple method that can be used by any one who does only an occasional transfusion.

1   (No agglutinin)   3   (1 agglutinin) "B"
(10 per cent of all persons)   (7 per cent of all persons)
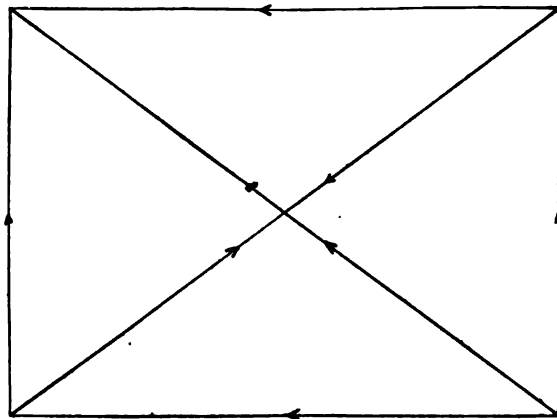
2   (1 agglutinin) "A"   4   (both agglutinins)
(40 per cent of all persons)   "A" + "B"
                                                                      (43 per cent of all persons)

Fig. 154.—Moss agglutination groups: The corpuscles of the various groups are agglutinated by the serums of the groups from which the arrows lead.

The old macroscopic method still used in many laboratories is accurate and is not objectionable except that it is time-consuming. This procedure, described in various texts (Bolduan, Kolmer, etc.), consists in mixing in a small test-tube a definite quantity of a suspension of washed corpuscles of the donor with three times the amount of the patient's serum and also in a similar manner the donor's serum with the patient's corpuscles. These tubes of cells and serums are incubated for two hours, being examined every few minutes for signs of iso-agglutinins or iso-hemolysis. At the end of two hours, if no agglutination or hemolysis has occurred, the transfusion is usually done, though some

men have advocated keeping the blood over night in an ice-box before
concluding that there is no incompatibility. Even a slight trace of
hemolysin in the patient's serum for the donor's corpuscles is objection-
able. However, it is a fact to be remembered, that hemolysis does not
occur unless it has been preceded by agglutination.

A modification of this is a micromacroscopic method, using capillary
tubes and small quantities of blood. This procedure is said to be more
quickly completed than the preceding one.

The microscopic methods can be carried out accurately and with
great saving in time. Recently Moss has published a description of the
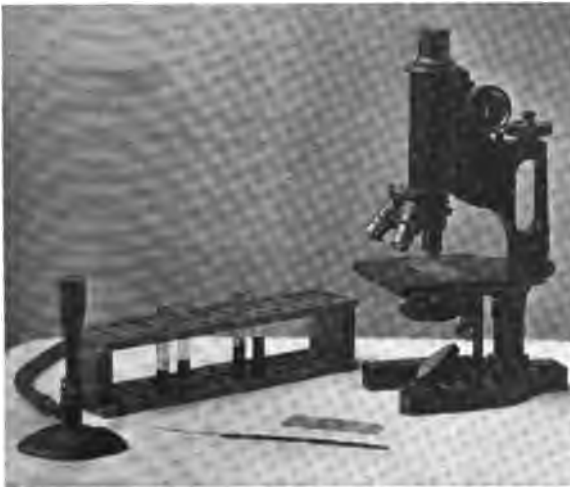
Fig. 155.—Apparatus: Microscope, "hanging-drop" slides and cover-slips, wire loop and burner (or alcohol
lamp), and tubes for serum and corpuscle-suspension.

method he is using. This necessitates the keeping on hand serum of
Groups 2 and 3. Hanging-drop preparations are made by mixing a
drop of suspension of the cells of the individual of the unknown group
with two drops of serum of Group 2; and another preparation is made,
using serum of Group 3. Agglutination with both serums places the
unknown in Group 1. If the Group 2 serum agglutinates the corpuscles,
the unknown is in Group 3, and if the corpuscles are agglutinated by
Group 3 serum, the unknown is in Group 2. If no agglutination occurs
after thirty minutes, the unknown is in Group 4. The serums of the
known groups may be preserved for a long time if kept sealed and sterile.

The method described by Brem more than a year ago is also micro-

'17—31

scopic and very similar to the Moss method, but it has, I believe, some advantages over the latter and is the simplest and safest one that we have. These two methods are essentially the same except that the corpuscle-suspensions of known groups, as well as serums, are used in the Brem technic. The technic as we have used it daily for more than a year is as follows:

It is necessary to have at hand serum- and corpuscle-suspension of either Group 2 or Group 3, and, if possible, of both. There being only a few individuals in Group 3, we always use this group, if possible, for testing unknown blood, as we have a greater chance of finding that the unknown is not in the same group.

Serum is obtained by collecting about 2 c.c. of blood in a dry sterile tube by vein-puncture or by sticking the finger, in the same manner

Fig. 156.—Microphotograph showing no agglutin-
ation of corpuscles.

Fig. 157.—Microphotograph showing agglutination
of corpuscles.

that we would collect blood for a Wassermann test. This blood is centrifugalized after separating the clot to obtain clear serum. The corpuscle-suspension is prepared by putting two or three drops of blood in 1 c.c. of a 2 per cent sodium citrate solution. These cells are not washed, but are used in their own citrated plasma. The slides for ex-amination are prepared by placing two drops of known serum (preferably Group 3) on a cover-slip by means of a sterile loop. After flaming the loop to remove the remnant of serum clinging to it, one loopful of the corpuscle-suspension of the unknown blood is added to the serum. The cover-slip is inverted over a hollow-ground slide, and the hanging drop is ready for microscopic examination. Another cover-slip and slide is then prepared, taking first two loopfuls of unknown serum, and then one loopful of known corpuscle-suspension. The slides are now examined with a microscope with a low-power objective and a high-power eye-

piece for agglutination of corpuscles in the hanging drop.   This usually
occurs almost at once.   Tipping the slide from side to side carefully so
as thoroughly to mix corpuscles and serum sometimes hastens the
end-result.   If there is no agglutination on either slide, the unknown
and the known are in the same group.   This will seldom be the case if
the known blood we are using is Group 3.   If there is agglutination in
both hanging drops, then our unknown is in the reciprocal group, that is,
Group 2.   If the known serum agglutinates the unknown corpuscles,
but unknown serum contains no agglutinin, then the unknown is in
Group 1.   We usually prove this by using both Group 2 and Group 3
serums with the unknown corpuscles, as agglutination should occur with
both.   No agglutination of the unknown corpuscles, but instant agglu-
tination of the known corpuscles, by the unknown serum, indicates that
we are examining blood of Group 4.   We prove this by testing with
corpuscles of both Group 2 and Group 3.   Agglutination should occur
with the cells of both of these groups.   By the Brem method the group
of an unknown may be determined in fifteen minutes or less, including
the time of bleeding the person and centrifugalizing the blood-serum.
With the Moss method in testing Group 4 individuals it is necessary to
wait thirty minutes before deciding that no agglutination has occurred
with the known serums and the unknown cells.   On the other hand,
with the Brem method agglutination occurs almost at once with the
known cells and the unknown serum.   As 43 per cent of persons are in
this group, it is evident that the latter method is time-saving when many
persons are being grouped, and it is on that account preferable.   There
is one disadvantage of the Brem method in comparison with the Moss
method, and that is in the fact that the suspension of red blood-corpus-
cles autolyzes in a few days.   It is advisable, therefore, to have available
a source for fresh samples of blood of both groups.

   Moss originally studied the grouping of 100 persons in series of 20
each, and determined that 10 per cent were in Group 1, 40 per cent in
Group 2, 7 per cent in Group 3, and 43 per cent in Group 4.   During
the past year we have kept a record of the group of 943 persons, of whom
318 were professional donors and 625 were patients.   Our percentages
for the four groups are as follows:

       Group 1...................................... 5.09 per cent
       Group 2...................................... 42.42 per cent
       Group 3...................................... 8.80 per cent
       Group 4...................................... 43.69 per cent

Our figures for Groups 2 and 4 are practically the same as those of Moss. We found in our series more Group 3 than Group 4 persons, which was not Moss' experience.

It is thought that the property of possessing iso-agglutinins that can be definitely classified is inherited, being governed by Mendelian laws. If both parents are in the same group, all offspring will be in that group. If the father is in one group and the mother is in another, the offspring may be in either group. In accordance with the studies of Landsteiner, Group 4 may be explained as a combination of Groups 2 and 3. We have seen a father in Group 2, a mother in Group 3, and a son in Group 4. It is an interesting speculation as to whether this may not be proof of Landsteiner's theory.

The question is often asked as to whether an individual may change his group, and it has been suggested that a patient should be retested after transfusion for a possible change in group. We are not in a position to state definitely that a person does not change his group; however, in the few cases of possible change in group that we have studied we are more willing to admit that some mistake had been made in our first test of the individual's blood than to assume that it had acquired new biologic properties as the result of transfusion. We have repeatedly examined the blood of a Group 1 individual, who has no agglutinin in his serum, and have found, after many transfusions with blood of all four groups, that he is still in Group 1.

The point is often raised by men who do only an occasional transfusion that it is not feasible to have at hand the necessary blood of known groups, and to go through the test as I have described it. This is true. However, it is a very simple matter to use Brem's method to determine whether a prospective donor's blood is suitable for the recipient, and not really know to which group either individual belongs. The technic for such a test would be as follows:

From the patient collect from 1 to 2 c.c. of blood in a dry sterile test-tube, and allow this to clot and the serum to collect, either from standing or being centrifugalized. In another small test-tube containing 1 c.c. of 2 per cent sodium citrate make a suspension of corpuscles with two or three drops of the patient's blood. In like manner prepare a tube containing the donor's serum, and another of the donor's corpuscle-suspension. With a clean wire loop mix two drops of the patient's serum with one drop of the donor's corpuscles on a cover-slip, and then two drops of the donor's serum with one drop of the patient's corpuscles

on another cover-slip. Make hanging-drop preparations by inverting over hollow-ground slides, and examine with the microscope. If, after waiting several minutes, there is no agglutination on either slide, it is evident that the donor and the patient are in the same group, and the operation may be performed. If the donor's serum agglutinates the patient's corpuscles, but there is no agglutination of the donor's corpuscles by the patient's serum, the transfusion may be safely done, knowing that the donor is not in the same group as the patient. But, if the patient's serum shows any agglutinin for the donor's corpuscles, then under no circumstances should that donor be used, but another individual should be selected for trial, and the test repeated. Except in actual emergency transfusions complement-deviation tests for syphilis should be made on the blood of donors.

In conclusion, I would repeat that in our experiences in a large number of transfusions in the past year we have found the Brem method exceedingly simple, time-saving, and accurate in the selection of donors; and also that the principles of this test can be applied by any one testing the recipient's blood directly with that of the prospective donor.

It should always be remembered that the essential thing in the selection of a donor is to be certain that the patient's serum will not agglutinate the donor's corpuscles (Figs. 156 and 157).

REFERENCES

1. Brem, W. V.: Blood-transfusion, with special reference to group tests. Jour. Am. Med. Assn., 1916, lxvii, 190–193.
2. Landsteiner, K.: Ueber Agglutinationserscheinungen normalen menschlichen Blutes. Wien. klin. Wchnschr., 1901, xiv, 1132–1134.
3. Moss, W. L.: Studies on iso-agglutinins and isohemolysins. Bull. Johns Hopkins Hosp., 1910, xxi, 63–70.
4. Moss, W. L.: A simplified method for determining the iso-agglutinin group in the selection of donors for blood-transfusion. Jour. Am. Med. Assn., 1917, lxviii, 1905–1906.

STUDIES ON CHOLESTEROL

III. THE INFLUENCE OF BILE DERIVATIVES IN BLOOR'S CHOLESTEROL DETERMINATION*

Preliminary Report

GEORGINE LUDEN

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The main object of the following communication was to determine whether bile derivatives were capable of giving the Liebermann reaction in the absence of cholesterol, and whether their color reaction could be destroyed by the use of sodium ethylate under conditions similar to those in Bloor's cholesterol determination.

The origin of the "brownish tint," well known to all who have made blood cholesterol determinations, and the relative merits of colorimetric and gravimetric methods for the determination of cholesterol, have been repeatedly discussed (Bloor, [2,3,4] Mueller, Weston). It will be remembered that Bloor, in the first publication of his new method,[2] specially mentions the addition of sodium ethylate to the ether-alcohol extract of the blood before evaporation, and that he left out the sodium ethylate in his modification of this method.[3] For brevity I shall refer to Bloor's original method as Bloor I and to its modification as Bloor II. The comments of Mueller on the Bloor method for cholesterol determination and Bloor and Knudson's reply[4] to these comments both refer to the Bloor II method only. Mueller's conclusions were that the values obtained by the Bloor method were increased by "other ether-alcohol- and chloroform-soluble substances" that were not cholesterol; that oxycholesterol might be among these substances; but that our knowledge of oxycholesterol is too indefinite to warrant positive conclusions. Bloor and Knudson claimed to show by a new procedure that there were either no other substances in the blood plasma, or that they behaved like ordinary cholesterol when treated with digitonin.

In connection with these statements a number of observations made by the writer since May, 1916, on a series of 748 parallel determinations with the Bloor I and II methods, may be of interest. The series com-

prises 374 different blood samples, including the blood of patients suffering from various diseases, the writer's blood in various experiments on nutrition, and the blood of goats used in an experiment that has already been published in part.[11] It does not include the 400 blood samples mentioned in the latter publication. It was found that in more than 100 specimens giving approximately normal cholesterol values, the difference between the Bloor I and II tests ranged from 0.050 to 0.070 mg., but in a group of samples secured from patients suffering from biliary disturbances, with and without icterus, it increased from 0.090 to 0.280 mg. The highest value with the Bloor II test was found in the blood of a highly icteric patient, and the deduction seemed admissible that it might be due to the presence of bile derivatives which the Bloor I tests had eliminated by the use of sodium ethylate.

Bile acids do not give the Liebermann-Burchard reaction,[6,8] but it seemed possible that a combination of bile-pigments and bile acids such as is often found in icteric blood, and usually in gallstones, might create conditions favorable for the reaction. The residue of gallstones from which the cholesterol had been thoroughly extracted (eleven successive extractions with boiling alcohol on the water-bath) was therefore selected for investigation. This residue dissolved readily in chloroform, with the exception of a black, dust-like sediment. The latter was collected on filter-paper, dried at room temperature, and used as the starting point for the experiments. It was dissolved in 2 per cent ammonia water and shaken out with pure chloroform in a separatory funnel. The chloroform was tested for cholesterol and remained colorless; however, as a measure of precaution, the operation was repeated three times. The third amount of chloroform having been drawn off completely, the aqueous alkaline solution of the black sediment was acidified drop by drop with concentrated hydrochloric acid and again shaken out with fresh chloroform. The latter assumed a deep yellow tone, and on addition of the Liebermann reagents (2 c.c. of acetic anhydrid and 0.1 c.c. of concentrated sulphuric acid to a 6 c.c. portion of the chloroform solution) gave a vivid green reaction such as is found only in strong cholesterol solutions; that is, 1 mg. to 1 c.c. of chloroform.

The amount of black sediment dissolved in the ammonia water had been extremely small,—only as much as could be held on the point of a small scalpel,—since the entire yield of black sediment had not exceeded 150 mg. and it had been necessary to make a great number of experiments before the most suitable method of extraction had been found.

An equally great number of experiments, in which sodium and potassium hydroxid had been used as solvents, had resulted in failure, showing that the relative alkalinity of the solvent was not without importance.

The color reaction obtained with the yellow chloroform extract of the bile derivatives must be considered a true Liebermann reaction, since it was produced by identical proportions of the same reagents used for cholesterol tests.

The absence of cholesterol in the yellow chloroform extract may be deduced from: (a) the insolubility of the black sediment in chloroform; (b) its solubility in ammonia water; (c) the repeated extraction of the aqueous alkaline solution with pure chloroform, which gave no Liebermann reaction although the procedure was practically identical with that of Autenrieth; and (d) the method by which the yellow chloroform extract giving the Liebermann reaction had been obtained, a method similar to that used for the recovery of bilirubin,[15] urobilin,[16] and cholic acid.[21] It had therefore been demonstrated that a positive Liebermann reaction may be obtained from a mixture of bile derivatives in chloroform solution in the definite absence of cholesterol.

Windaus[20] states that Liebermann's cholesterol reaction is characterized by a sequence of brilliant colors, vivid pink, blue, and dark green. This color reaction could be observed in all of these bile derivative solutions even when they contained as little as 0.020 mg. in 6 c.c. of chloroform, but I have been unable to find any trace of the pink or the blue stage of the reaction in cholesterol solutions such as are commonly used for blood cholesterol determinations (0.4 mg. in 6 c.c. or 0.5 mg. in 5 c.c. of chloroform). Since only the green stage of the reaction can be seen in cholesterol solutions of the above concentration, it was decided to ascertain how great the concentration of cholesterol solutions would have to be, the usual proportions of the reagents being maintained, in order to show the color sequence described by Windaus. It was found that neither the pink nor the blue stage could be observed in cholesterol solutions exceeding the concentration of standard tests from 10 to 400 times (Table 1). Nor could the color sequence described by Windaus be made visible by using one-half or one-quarter of the amount of the reagents.

For brevity, the bile derivative solutions used in my experiments will be referred to as "pigment solutions" and the uniform solution with which the following tests were made as "Pigment 28 solution." The latter contained 0.2 mg. of bile derivatives in every 6 c.c. of chloroform.

TABLE 1.—*Color Reactions in Cholesterol Solutions**

Test 1.—6 c.c. of our stock solution, namely, 6 mg. of cholesterol in 6 c.c. of chloroform; usual reagents added.

Reaction.—The colorless solution becomes dark green in a few seconds; no trace of the pink or the blue stage.

Test 2.—10 mg. of cholesterol in 6 c.c. of chloroform; usual reagents added.

Reaction.—Identical with Test 1, except that the green color appears almost black.

Test 3.—15 mg. of cholesterol in 6 c.c. of chloroform; usual reagents added.

Reaction.—The blue stage appears for a few seconds only and is blotted out by the density of the green stage. The solution appears black; its green tone can be recognized only in a very strong light.

Test 4.—200 mg. of cholesterol dissolved in 6 c.c. of chloroform; usual reagents.

Reaction.—As the sulphuric acid is added, its progress toward the bottom of the test-tube is shown by a streak of purple-violet, but the next second the whole of the solution has turned black-green. Its green color can be recognized only near the top edge by shaking the test-tube.

Apart from the color sequence referred to above, the pigment solutions showed the following peculiarities, which distinguished them from pure cholesterol solutions: (*a*) Their reaction was much slower than that of cholesterol; (*b*) the green stage of the reaction was olive-green, as compared with the emerald-green of pure cholesterol; (*c*) the green stage persisted unchanged from three to four times as long as the cholesterol green in solutions of equal strength; and (*d*) colorimetric determinations showed that the color value of the green stage was only a little over one-half of the cholesterol green in solutions of equal concentration, although, owing to the difference in tone, it appeared to be greater in the test-tube. In reference to these peculiarities the term "bile-green reaction" in the Liebermann test is tentatively suggested for the color reaction of these cholesterol-free bile derivatives.

A series of observations and systematic tests proved that the usual

* The standard cholesterol solution used in all our blood cholesterol determinations contains 0.4 mg. of cholesterol in 6 c.c. of chloroform. It is made up from a stock solution containing 200 mg. of cholesterol (Merck) in 200 c.c. of chloroform.

Both standard and stock solutions are sealed with paraffin and kept on ice when not in use, in order to prevent any evaporation of the chloroform; the latter would increase their concentration, thereby affecting the accuracy of the tests.

Standardized graduated pipets are used in all our tests in preference to graduated cylinders, since the latter often vary slightly and give less accurate results in consequence.

cholesterol standard test (0.4 mg. of cholesterol in 6 c.c. of chloroform) reached its maximum color value at room temperature (20–22 C.) in five to six minutes, and maintained it for approximately thirty minutes; that the test lost one-third of its color value in eighty minutes and became colorless, that is, pale yellow, in six to seven hours. On the other hand, pigment solutions of identical concentration reached their maximum color value in one hundred and ninety minutes and remained unchanged for at least twenty-four hours. A record was kept of the exact time at which the reagents were added to the tests and revealed the length of the duration of the pink, blue, and green stages of the reaction in the pigment solutions at a room temperature of 20–22 C. (Table 2). In every instance freshly made "ripe" standard tests not more than twenty minutes old were used for comparison. The advantage of making cholesterol determinations at room temperature rather than at a temperature of 35–37 C. has been discussed.[11] Previous observations on the rapid reaction found in many pathologic blood samples have been fully corroborated by subsequent findings.

TABLE 2.—*Color Reactions in Pigment Solutions*

2 c.c. of acetic anhydrid and 0.1 c.c. of concentrated sulphuric acid added to each 6 c.c. test. Room temperature, 20–21 C.

Test 1.—1.2 mg. in 6 c.c. of chloroform. Pigment 28 solution undiluted (three tests).
Reaction.—The test solution turns bright reddish pink immediately. The pink color lasts for twenty minutes. The test-tube is plunged in very hot water for a few seconds. The blue stage of the reaction appears, but has a dirty violet-blue tone. It is followed in three to four minutes by the green stage, intense olive-green, which seems to be as dark as, if not darker than, cholesterol green of equal strength in the test-tube.
Color Value.—

After 30 minutes equal to 0.500 mg. cholesterol. (Standard cholesterol test* 0.400 mg.)
"   6 hours   "   " 0.666   "   "
"   24   "   "   " 0.666   "   "
"   48   "   "   " 0.666   "   "
"   72   "   faded to a dirty brown.

Test 2.—0.400 mg. in 6 c.c. of chloroform (five tests).
Reaction.—The test solution turns bright vivid pink immediately. The pink color lasts for five to seven minutes. Dirty violet tone for three to four minutes. Olive-green.

* A newly made "ripe" standard was used for every determination, and for every test the Duboscq colorimeter was set at 10.0 mm.

Color Value.—

After 20 minutes equal to 0.180 mg. cholesterol.   (Standard cholesterol test 0.400 mg.)
"   1 hour   "   " 0.200 "   "
"   3 hours   "   " 0.200 "   "
"   24   "   "   " 0.222 "   "
"   48   "   faded to a dirty brown.   (Standard cholesterol test fades to dirty yellow
in six hours.)

Test 3.—0.120 mg. in 6 c.c. of chloroform (three tests).

Reaction.—Vivid pink for five minutes.   Intermediate stage hard to define.   Green in ten minutes.

Color Value.—

After 30 minutes equal to 0.060 mg. cholesterol.   (Standard cholesterol test 0.400 mg.)
"   3 hours   "   " 0.056 "   "
"   24   "   faded to dirty yellow.

Test 4.—0.080 mg. in 6 c.c. of chloroform (three tests).

Reaction.—Clear pale pink for three minutes.   Intermediate color cannot be recognized.   Clear but light olive-green in six to eight minutes.

Color Value.—

After 30 minutes equal to 0.050 mg. cholesterol.   (Standard cholesterol test 0.400 mg.)
"   3 hours   "   " 0.040 "   "
"   24   "   faded to pale dirty yellow.

Test 5.—0.040 mg. in 6 c.c. of chloroform (three tests).   (Standard cholesterol test, 0.400 mg.)

Reaction.—Clear pale pink; then pale olive-green which lasts for about three hours.

Color Value.—Cannot be determined as the test looks gray in the colorimeter when compared with the emerald-green standard, although its color is clear pale green in the test-tube.

Test 6.—0.020 mg. in 6 c.c. of chloroform (three tests).   (Standard cholesterol test, 0.400 mg.)

Reaction.—Faint but distinct pink; then very pale olive-green lasting about one hour.

Color Value.—Cannot be determined, for the same reasons as in Test 5.   The green color is also clearly visible in the test-tube.

In order to study the effects of sodium ethylate on the cholesterol-free bile derivatives under conditions parallel to those found in the Bloor method, the following experiments were made:

The chloroform of a portion of the Pigment 28 solution was evaporated and the orange-colored residue extracted with ether-alcohol in the manner described by Bloor for blood samples.   One portion of the ether-alcohol extract was treated according to the Bloor I method, with sodium ethylate, and the other according to the Bloor II method, without

sodium ethylate. Overheating was carefully avoided during evapora-
tion. After the usual extraction of the residue with chloroform, the
Bloor I test was colorless and remained colorless when the usual reagents
were added, even when the test was warmed. The Bloor II chloroform,
on the contrary, was deep yellow, and on the addition of the reagents
gave the brilliant bile-green reaction already described. The experiment
was repeated four times and gave identical results in every instance.
Parallel tests made with pure cholesterol solutions treated in exactly the
same way gave positive Liebermann reactions, both with the Bloor I
and the Bloor II methods. A slight loss of color value occurred in the
pigment as well as in the cholesterol control tests. In the latter it was
so small that it may be considered merely technical; 0.233 and 0.572
mg. of cholesterol were recovered when 0.240 and 0.600 mg. had been
used respectively. In the former the loss was somewhat greater, but the
factors which caused it cannot be considered at present. The experi-
ments showed conclusively, however, that the color reaction of choles-
terol-free bile derivatives can be destroyed by sodium ethylate, whereas
that of true cholesterol is not similarly affected. It should be added
that the bile derivatives were readily soluble in ether, alcohol, chloro-
form, and petroleum ether,[14] but that a precipitate was formed when-
ever sodium ethylate was added to the chloroform solution, whereas in
the other solvents precipitation was barely perceptible. The bile-green
type of Liebermann reaction could be obtained also with the usual
reagents from the opaque residue left in the beakers used for the Bloor I
tests after chloroform extraction by dissolving the residue in acid chloro-
form. These findings seem to support the deduction that the formation
of a chloroform-insoluble sodium salt of bile derivatives may account
for the difference observed in the Bloor I and Bloor II samples, and that
the potassium salts of these substances may be more readily soluble in
chloroform, especially in the presence of water. The occurrence of the
brownish color in some of the Autenrieth tests and Mueller's* observa-
tions might also be explained thereby.

Although these experiments showed that the color reaction of bile
derivatives obtained from gallstones can be destroyed by sodium ethy-
late, it remained to be proved that closely allied or identical bodies were

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* The brownish color does not appear in every sample treated by the Autenrieth
method, and I am unable to agree with Mueller's statement that it is "invariably present"
in Bloor II tests. On the contrary, one-third of our determinations gave a brilliant green
reaction that could be matched easily with the standard solution. Tests made by the
Bloor I method always gave a perfect match.

responsible for the high values found in icteric blood by the Bloor II method. The isolation of the bile derivatives in icteric blood proved extremely difficult, probably owing to the relatively small quantities in which they are present. Thirty attempts to isolate them were unsuccessful. It is possible that these failures may be explained by the observations of Hoover and Blankenhorn on "dissociated jaundice" and that several of the samples used in my experiments contained only bile acids. However, there may be other reasons connected with the various stages of oxidation described by Lifschütz,[6-10] but these cannot be discussed at present.*

At last a simple method was found by which the bile derivatives of icteric blood could be isolated: 6 c.c. of icteric blood were extracted with ether-alcohol according to the Bloor method. The extract was partly evaporated at room temperature. The remaining portion of the solvent, in which cholesterol crystals could be observed microscopically, was poured off. A black, crust-like ring which had formed where the liquid receded during evaporation was dissolved in 2 per cent ammonia water, and the aqueous alkaline solution filtered, acidified, and shaken out with chloroform. The chloroform assumed a yellow tone and gave the bile-green type of Liebermann reaction. The bile derivatives, in this specimen of icteric blood at least, must therefore have been closely allied, if not identical with, the cholesterol-free bile derivatives obtained from gallstones. The difference between the Bloor I and Bloor II tests of this sample had been 0.280 mg. in the colorimetric determination for blood cholesterol.

A test devised by Lifschütz† for the differentiation between oxycholesterol and oxidized cholic acid proved of great value in establishing the identity of the bile derivatives in question. This test will be referred to as Lifschütz' "differential test." It is based on the relative solubility of oxycholesterol and oxidized cholic acid in chloroform and glacial acetic acid, and should not be confounded with the oxycholesterol color reaction. Lifschütz states that the oxycholesterol color reaction can be obtained alike in glacial acetic solutions of pure cholesterol, pure cholic acid, and ordinary bile after oxidation with benzoyl peroxid and the subsequent addition of eight drops of concentrated sulphuric acid and one drop of ferric perchlorid (2 per cent solution in glacial acetic acid)

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* Because of Lifschütz' observations on the decomposition of cholesterol to bile acids, and Schulze and Winterstein's studies on the influence of the light on cholesterol, my pigment solutions have always been kept in the dark.

† Lifschütz,[9] p. 346.

to every 1 c.c. portion of the test.   If an equal volume of chloroform is added to the glacial acetic solutions, the green color of the oxidized cholesterol will be found in its entirety in the upper layer, the bottom layer being practically colorless (pale yellow or brownish), whereas if the test is made with oxidized cholic acid the colors will be reversed, the upper stratum will remain colorless after separation, and the bottom (chloroform) layer will contain all the green color.   When bile is used, both layers will be colored in direct proportion to the amount of either substance present in each layer; the quantity can then be determined only spectroscopically, by means of the characteristic spectra.   In the absence of spectroscopic facilities, however, oxycholesterol and oxidized cholic acid can be differentiated accurately by means of the differential test when only one substance is present in the solution.   Lifschütz adds that the proportions he recommends must be strictly observed in order to obtain the above results.   These proportions have therefore been used in the following experiments.

The chloroform component of—(a) A cholesterol solution; (b) a portion of the Pigment 28 solution, and (c) a solution containing the cholesterol-free bile derivatives of icteric blood, was removed by evaporation and the residues were dissolved in glacial acetic acid.   The glacial acetic solutions were treated in the manner described by Lifschütz and the differential test was made by adding an equal volume of chloroform. After separation had taken place the green color of the oxidized cholesterol was found in the upper layer, while the bottom layer had a faint pinkish brown tinge.   In the two tests made with the bile derivatives, on the contrary, the upper layers were colorless and the green color could be seen in its entirety in the lower (chloroform) layers. Whether the differential test was made at the red, the blue, the green, or the terminal dirty brown stage of the reaction, the color component of the oxidized cholesterol was found in the upper stratum, whereas that of the bile derivatives invariably settled in the bottom layer.   Moreover, the green stage of the bile derivatives remained unchanged for days, while the oxycholesterol green changed to dirty brown in about twelve hours.   The latter peculiarity alone, which is in accordance with the color persistency of the bile-green reaction in my pigment solutions, might suffice to distinguish the bile derivatives from oxycholesterol, and recalls Lifschütz' statement concerning the color reaction of oxidized cholic acid, that colors like spectra remain for weeks.   Although these tests showed that the bile derivatives contained no oxycholesterol, but

substances that were closely allied to cholic acid, a slight difference could be observed between the derivatives from gallstones and those from icteric blood. The latter needed the complete oxidation required by cholic acid, while the former gave the Lifschütz reaction after oxidation with benzoyl peroxid alone, without the addition of sulphuric acid and ferric perchlorid. It will be remembered that the color sequence of the Lifschütz reaction is the reverse of that seen in bile-pigments under the influence of oxidizing agents.* The gallstone derivatives must therefore have been partially oxidized. It is hard to understand where this partial oxidation could have occurred, as no oxidizing agents except the atmospheric oxygen during extraction of the cholesterol had been used until Lifschütz' differential test was made. The following explanation is tentatively suggested: As bilirubin, a hemoglobin derivative (Mathews), could be demonstrated in the mixture by Hammarsten's test, and as Lifschütz[10] was able to prove the strongly oxidizing properties of hemoglobin, it seems possible that some of the bile-pigments present in the mixture may have played a part in the partial oxidation of the cholic acid which it contained. The bile derivatives from icteric blood exhibited the following peculiarity: Although the upper layer remained colorless in Lifschütz' differential test, the colored bottom layer was composed of two strata, the lower and narrower being dark green, the other bright yellow with a green tinge. This showed that the bile derivatives did not contain oxidized cholic acid alone, but another closely allied substance as well. The latter may have been the "rhizocholic acid" mentioned by Mathews† or the "resin acid" described by Minovici and Zenovici.

Further investigations concerning the solubility of the bile salts, spectroscopic determinations, and tests with Rosenheim's new reaction for oxycholesterol will be reported when completed.

Summary

1. In 748 parallel blood cholesterol determinations by Bloor's original method with sodium ethylate (Bloor I) and its modification without sodium ethylate (Bloor II), a constant difference was observed in the cholesterol values obtained, lower values being registered by the Bloor I method.

2. In normal blood a constant slight difference (0.050 to 0.070 mg.)

* Von Reinbold,[15] p. 278.   † Mathews,[12] p. 430.

occurs between the values obtained by the Bloor I and Bloor II methods; in icteric blood differences of 0.090 to 0.280 mg. occur.

3. Since the Liebermann reaction could be obtained with a mixture of cholesterol-free gallstone derivatives, the difference appears to be due to a combination of bile-pigments and bile acids present in the blood.

4. The Liebermann reaction of cholesterol-free gallstone derivatives differs from that of cholesterol inasmuch as the pink stage of the reaction is distinctly visible in weak solutions of the former, although it cannot be seen in cholesterol solutions of equal or up to 400 times greater concentration.

5. The type of Liebermann reaction given by gallstone derivatives can be obtained from the cholesterol-free residue of icteric blood.

6. This color reaction is destroyed by the use of sodium ethylate under conditions parallel to those found in the Bloor I method. The color reaction of cholesterol is not affected by the use of sodium ethylate.

7. That the Liebermann reaction of cholesterol-free bile derivatives is due, not to oxycholesterol, but to cholic acid and allied substances in the presence of bile-pigments, could be proved by Lifschütz' differential test.

8. Cholesterol-free gallstone derivatives require less vigorous oxidation than bile derivatives from icteric blood in order to give Lifschütz' differential test.

9. The oxidizing properties of hemoglobin having been demonstrated by Lifschütz, and bilirubin, a hemoglobin derivative, being demonstrable in the gallstone derivatives, it is tentatively suggested that the bile-pigments contained in the latter may have caused their partial oxidation.

10. The experiments suggest that parallel determinations with Bloor's original method and its modification may furnish valuable information concerning the chemical constituents of the blood in cases of biliary disturbance with and without icterus, which might be supplemented by the dialyzation method of Hoover and Blankenhorn.

REFERENCES

1. Autenrieth, W., and Funk, A.: Ueber kolorimetrische Bestimmungsmethoden: Die Bestimmung des Gesamtcholesterins im Blut und in Organen, Münch. med. Wchnschr., 1913, i, 1243–1248.
2. Bloor, W. R.: Studies on blood fat. II. Fat absorption and the blood lipoids, Jour. Biol. Chem., 1915, xxiii, 317–326.
3. Bloor, W. R.: The determination of cholesterol in blood, Jour. Biol. Chem., 1916, xxiv, 227–231.

4. Bloor, W. R., and Knudson, A.: The separate determination of cholesterol and cholesterol esters in small amounts of blood, Jour. Biol. Chem., 1916, xxvii, 107–112.
5. Hoover, C. F., and Blankenhorn, M. A.: Dissociated jaundice, Arch. Int. Med., 1916, xviii, 289–303.
6. Lifschütz, J.: Die Oxydationsprodukte des Cholesterins in den tierischen Organen. III. Mitteilung, Ztschr. f. physiol. Chem., 1908–09, lviii, 175–184.
7. Lifschütz, J.: Die Oxydationsprodukte des Cholesterins in den tierischen Organen (Pfortader-Lebervene). V. Mitteilung, Biochem. Ztschr., 1913, lii, 206–210.
8. Lifschütz, J.: Der Abbau des Cholesterins in den tierischen Organen (Studie). VI. Mitteilung. (Cholesterin-Gallensäuren), Ztschr. f. physiol. Chem., 1914, xci, 309–328.
9. Lifschütz, J.: Die Abbauprodukte des Cholesterins in den tierischen Organen (Gallensäuren). VII. Mitteilung, Ztschr. f. physiol. Chem., 1914, xcii, 383–401.
10. Lifschütz, J.: Die Oxydation des Cholesterins durch das Blutgewebe. VIII. Mitteilung, Ztschr. f. physiol. Chem., 1914–15, xciii, 209–227.
11. Luden, G.: Observations on the changes in the cholesterol content of the blood of goats following cholesterol feeding alone, roentgen treatment alone, and cholesterol feeding combined with roentgen treatment and subsequent castration, Jour. Biol. Chem., 1916, xxvii, 273–295.
12. Mathews, A. P.: Physiological Chemistry, New York, 1915.
13. Minovici, S., and Zenovici-Eremie, T.: Some new oxidation products of cholesterol, Bull. sect. sci. acad. romaine, 1915, iv, 194–205 (abstracted in Chem. Abst., 1916, x, 606–607).
14. Mueller, J. H.: A comparison of the results obtained by colorimetric and gravimetric determinations of cholesterol, Jour. Biol. Chem., 1916, xxv, 549–560.
15. Von Reinbold, B.: Urobilin. In Abderhalden, E., Biochemisches Handlexikon, Berlin, 1911, vi, 278.
16. Von Reinbold, B.: Urobilin. In Abderhalden, Biochemisches Handlexikon, Berlin, 1911, vi, 288–290.
17. Rosenheim, M. C.: A new colour reaction for "oxycholesterol," Biochem. Jour., 1916, x, 176 (abstracted in Chem. Abst., 1916, x, 3081).
18. Schulze, E., and Winterstein, E.: Über das Verhalten des Cholesterins gegen das Licht, Ztschr. f. physiol. Chem., 1904–05, xliii, 316–319. (Cited by Lifschütz.)
19. Weston, P. G.: Colorimetric methods for determining serum cholesterol, Jour. Biol. Chem., 1916–17, xxviii, 383–389.
20. Windaus, A.: Cholesterin. In Abderhalden, Biochemisches Handlexikon, Berlin, 1911, iii, 270.
21. Windaus, A.: Cholsäure (früher Cholalsäure). In Abderhalden, Biochemisches Handlexikon, Berlin, 1911, iii, 315.

NOTE.—Owing to lack of space, Study IV, experiments concerning the relation of the diet, the blood cholesterol, and the "lymphoid defense," which appeared in the Jour. Lab. and Clin. Med., 1917, iii, 141–174, will not be published in this volume.

STUDIES ON CHOLESTEROL

V. THE BLOOD CHOLESTEROL IN MALIGNANT DISEASE AND THE EFFECT OF RADIUM TREATMENT ON THE BLOOD CHOLESTEROL*

GEORGINE LUDEN

Between November, 1915, and December, 1917, a total of 1,069 samples were tested for cholesterol. The above figure includes 1,052 determinations on blood cholesterol (human, goat, gopher, and dog), 14 determinations on foodstuffs and 3 on human pus. Of 743 blood samples parallel determinations in triplicate were made according to Bloor's original method (Bloor 1 with sodium-ethylate) and its modification (Bloor II, with sodium-ethylate), making a total of 4,458 determinations with Bloor's tests. The advantage of these parallel determinations by which the amount of cholesterol split-products present in the blood is revealed, was shown by 2,196 tests made on pathologic human blood, including blood in 70 miscellaneous conditions, 41 cases of pernicious anemia, 37 of exophthalmic goiter, 3 of myxedema tested 18 times at various intervals during the administration of the thyroid hormone (Kendall's thyroxin), 79 determinations on the writer's own blood as normal control, 9 cases of sarcoma (16 determinations), and 92 determinations of the blood cholesterol in cases of carcinoma before and after radium treatment, including 20 weekly determinations on one patient.

The blood cholesterol values in carcinoma were found to be high in 43 per cent of 72 patients and in 56 per cent of 55 patients that were to have radium treatment. In the latter, 54 per cent showed equal values with the Bloor I and Bloor II tests, which indicated some disturbance of cholesterol metabolism in carcinoma, since a difference between the values obtained by the two methods is always found normally, and no equal values were found in 252 determinations on non-malignant cases. After radium treatment the equal values were found to disappear, and

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the percentage of high values dropped to 12 in 17 patients. In sarcoma the blood cholesterol values were found to be very much lower than in carcinoma, equal values were observed in two cases and the effect of radium was similar to that observed in carcinoma.

In myxedema high cholesterol values (but not equal values) were found and the administration of the thyroid hormone brought the blood cholesterol back to normal at a rate parallel to the rise in basal metabolism which it induced.

These observations seem to warrant the following conclusions:

1. That the high blood cholesterol values found in carcinoma are not due to cell destruction, since they are lowered by radium treatment although radium causes cell destruction, but that they are due to a disturbance of cholesterol metabolism.

2. That the disturbance of cholesterol metabolism may be but evidence of a low rate of basal metabolism, since the high cholesterol values in myxedema are reduced by the administration of the thyroid hormone by which the rate of basal metabolism is greatly increased.

3. That radium treatment, by lowering the blood cholesterol values, alters the chemical composition of the blood, a fact which has not hitherto been taken into account in the study of the effects of radium treatment.

4. That the administration of the thyroid hormone affects the blood cholesterol values in a manner similar to that of radium treatment and may therefore be expected to be equally beneficial to patients suffering from carcinoma. However, careful investigation will be needed before definite conclusions can be drawn concerning the effect of thyroxin in carcinoma.

HEMOLYTIC JAUNDICE: A REVIEW OF SEVEN-TEEN CASES*

H. Z. GIFFIN

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From June 30, 1911, to September 13, 1916, 17 patients with hemo-lytic jaundice were under observation. The disease is of comparatively rare occurrence and may be easily mistaken for other conditions. Twelve of the patients were splenectomized; five were medical. Ten were men and seven were women, and their occupations were exceedingly varied. The youngest patients were nine, thirteen, and nineteen years of age, respectively, and the oldest forty-nine years. Between the ages of twenty and thirty there were eight patients, and between thirty and forty there were five, the largest number presenting themselves between the ages of twenty and thirty years. Leukemia, pernicious anemia, and hemophilia were noticeably absent in the family histories.

Jaundice.—Seven of the 17 patients had been jaundiced from infancy. Four others had been jaundiced since childhood, and 4 had an onset between the ages of eighteen and twenty-two years. It is quite probable that in at least 10 of the entire series the disease should be classified as congenital in type. There is also evidence that in some of the patients who had had an onset between the ages of eighteen and twenty-two years the condition should be regarded as congenital. In clinical characteristics and severity, the symptoms corresponded to the con-genital type. Moreover, an increased fragility of the erythrocytes in close relatives of patients of this age was demonstrated in two instances. Three cases were definitely familial; 6 others gave very suggestive histories of familial jaundice. One patient had a history of the onset of jaundice at the age of thirty-two, and another as late as forty-six years of age. These were severe cases of the acquired type. The jaundice in all the cases of this series was acholuric and seems never to have completely disappeared. It was remittent rather than intermittent. A tinge of yellow was said to remain after crises and to be present at all

times. Several of our patients have stated that their jaundice was increased by excitement and nervousness. In all the 12 operative cases the jaundice was marked. In one patient with complications a trace of bile was at times present in the urine. Undoubtedly very mild cases occur in which the jaundice may be easily overlooked. The jaundice may also be of very mild grade early in the history of a given case. Pruritus was noted in only one patient in spite of the frequent complication of cholelithiasis.

Splenomegaly.—In 12 of the 17 patients the spleen had been palpated previous to our examination. In one patient it had been easily palpable since infancy, and in another since the age of seven years. Others had been recognized as long as ten and fifteen years previous to the examination. All were easily palpable at the time of examination. Mild cases of hemolytic jaundice occur without an appreciable enlargement of the spleen. I have observed two patients with histories very suggestive of a mild grade of the disease, and spleens merely palpable, in whom there was an increased fragility of the erythrocytes in the peripheral circulation. On the other hand, the spleen in definite cases may be very large, though it is never as enormous as the spleen of leukemia or splenic anemia. In our 12 operative cases it varied from 300 grams to 1780 grams, giving an average of 1070 grams, five or six times the normal size. In all of the non-operative cases the spleen was appreciably enlarged.

Enlargement of the liver.—Two of the 5 non-operative cases presented evidence of enlargement of the liver. In 1 of these it was marked. Eight of the 12 operative cases showed enlargement of the liver at operation, and in 2 of these a surgical diagnosis of cirrhosis of the liver was made. The cirrhoses were of the granular rather than the lobulated type and of slight degree. The livers were not contracted. One patient only—an operative case—showed evidence of abdominal fluid; the amount of fluid was small. The liver was much congested, but a positive diagnosis of cirrhosis could not be made. Two patients with a severe acquired type of the disease presented upon exploration very large livers. Two patients with a congenital type of the disease and very large spleens, 1250 grams and 1780 grams respectively, had livers which were apparently normal.

Crises.—Sixteen of the 17 patients gave a history of attacks, some very mild in character, of abdominal distress, nausea, fever, vomiting, and headache, and when gallstones were present, of seizures of severe pain. Usually these crises were mild during childhood and more severe

TABLE 1.—BLOOD COUNTS IN 12 CASES OF HEMOLYTIC JAUNDICE: SPLENECTOMY

Case	Time Before and After Splenectomy	Hemoglobin Per Cent	Red Blood-Cells Millions	Color Index	Normoblasts °	Megaloblasts °	Miscellaneous Findings	White Blood-Cells	Polymorpho-nuclears Per Cent	Small Lymphocytes Per Cent	Large Lymphocytes Per Cent	Eosinophils Per Cent	Basophila Per Cent	Myelocytes Per Cent
1 (28194)	2 days before	65	3.29	0.9+	3	0	0	10000	72.3	23.0	3.7	0.7	0	0.3
	20 days after	85	4.80	0.8+	0	0	0	9200	76.0	15.0	4.5	3.0	1.5	0
	3 months after	89	4.52	0.9+	0	0	0	15400	55.5	35.0	3.5	0.5	0.5	0
2 (80218)	9 days before	58	3.09	0.9+	0	0	...	7400	79.7	16.3	0.3	2.7	1.0	0.3
3 (112836)	8 days before	40	1.74	1.1	26	0	Anisocytosis	9500	74.7	15.3	2.3	6.0	1.3	0.7
	29 days after	35	1.80	0.9+	203	1	Anisocytosis	26400	77.3	15.7	4.3	1.0	1.0	
	14 months, 20 days after	80	3.77	1.0+	0	0	0	8000	58.0	31.0	9.0	2.0	0	0
	20 months, 14 days after	96	2.12	0.8+	143	3	Anisocytosis, poikilocytosis	22600	68.0	21.7	6.3	2.3	1.3	0.3
4 (135948)	7 days before	79	4.32	0.9+	0	0	Anisocytosis, polychromatophilia	19400	78.0	15.0	4.0	3.0	0	0
5 (141268)	9 days before	24	1.34	0.8+	57	0	Anisocytosis, poikilocytosis, granular degeneration, polychromatophilia	15200	59.0	29.0	4.0	2.3	2.7	3.0
	18 days after	38	2.16	0.8+	0	0	Anisocytosis, polychromatophilia	12600	64.7	16.3	10.7	6.7	1.7	0
6 (142074)	1 month before	50	3.60	0.7	0	0	Anisocytosis, polychromatophilia	10800	78.3	19.3	2.0	0.3	0	0
	16 days after	69	4.28	0.8+	0	0	0	6900	56.7	35.0	3.3	4.3	0.7	0
7 (148510)	7 days before	58	3.28	0.8+	0	0	Anisocytosis, poikilocytosis	7700	65.3	28.7	5.3	0	0.7	0
8 (153945)	6 days before	47	2.84	0.8+	0	0	Anisocytosis	9800	76.7	14.7	6.0	2.3	0.3	0
9 (148309)	29 days after	60	4.88	0.6+	0	0	0	11600	50.7	30.3	4.3	13.0	1.7	0
	13 days before	80	5.00	0.8+	0	0	0	7900	57.7	33.0	8.7	0.7	0	0
	4 days after	82	5.12	0.8+	0	0		13400	67.7	21.3	8.7	2.0	0.3	0

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No.	Date														
10 (161538)	7 days before	64	3.86	0.8+	0	0	Anisocytosis, poikilocytosis, polychromatophilia	0	6400	75.7	20.3	3.3	0.3	0.3	0
11 (162670)	21 days after	70	4.68	0.7+	0	0	Anisocytosis, poikilocytosis, polychromatophilia	0	8100	55.0	37.7	4.3	1.3	1.7	0
	9 days before	67	3.65	0.9+	0	0			12200	62.3	32.0	1.7	4.0	0	0
12 (94675)	20 days after	80	4.22	0.9+	0	0	Anisocytosis, poikilocytosis, polychromatophilia	0	12400	53.7	37.0	7.3	2.0	0	Few
	8 days before	69	3.34	1.0+	0	0			9800	73.3	23.3	2.3	0.7	.03	0
	33 days after	73	4.76	0.7+	0	0	Anisocytosis, poikilocytosis	0	16800	80.0	13.7	4.7	1.3	.03	0

BLOOD COUNTS IN FIVE CASES OF HEMOLYTIC JAUNDICE: NON-OPERATIVE

No.															
13 (91298)	:	90	4.76	0.9	0	0	Anisocytosis, poikilocytosis	0	3700	67.0	30.7	0.7	1.3	0.3	0
14 (153653)	:	60	3.90	0.8+	0	0		0	:	:	:	:	:	:	:
15 (157525)	:	80	4.92	0.8—	0	0		0	5800	45.0	38.7	14.3	0.7	1.3	0
16 (169405)	:	84	4.88	0.8+	0	0		0	6000	69.0	19.0	9.0	1.0	2.0	0
17 (172287)	:	83	5.06	0.8+	0	0		0	8200	:	:	:	:	:	:

* Number of cells seen while counting 300 leukocytes.

NOTE.—Differentials are based on a count of 300 cells.

in later life. In cases of short duration they were milder than in cases of long duration. The patient who gave a history of no crises did, however, complain of attacks of extreme weakness. The most important evidence that can be obtained from the history in arriving at a differential diagnosis of hemolytic jaundice is recurrences of deepening jaundice with crises.

The blood-picture.—In these patients histories of severe recurrent anemia were not obtained. In 2 instances only was the anemia severe. In a majority of the cases it was of moderate degree and chronic type. The hemoglobin in the 12 cases varied from 24 per cent to 86 per cent, and averaged 59 per cent. In the entire group of 17 cases the lowest erythrocyte count was 1,340,000. In 2 patients the counts were between 1,000,000 and 2,000,000, in one between 2,000,000 and 3,000,000, and in 7 between 3,000,000 and 4,000,000. The color index was, as a rule, high. In 2 instances it was more than 1.0; in 5 it was 0.9+, and in 9 it was 0.8+. The uniformly high color index is quite definitely indicative of the myelotoxic factor in the disease. Normoblasts were present in 3 patients and megaloblasts in 1. Nine patients showed slight or moderate deformity and degeneration of the erythrocytes. Leukocyte counts revealed an absence of leukopenia and a tendency to slight leukocytosis. The leukocyte count just prior to operation varied from 6400 to 19,400 and averaged 10,950. Differential counts were not distinctly abnormal; there was an absence of lymphocytosis. After splenectomy there was, as a rule, a very prompt increase in the hemoglobin estimation and the red-cell count. Post-operative leukocytosis was noted, but it was not a constant finding. In a majority of the cases after splenectomy there was an increase in the relative percentage of small lymphocytes and a decrease in polymorphonuclears. The reverse has been noted in our cases of pernicious anemia after splenectomy; that is, the blood has shown an increase of polymorphonuclears.

The condition of the blood was reported as normal in 9 of 10 living patients from two months to five and one-half years after operation. However, in only a few of these patients has it been possible to obtain complete blood counts. In the tenth patient the hemoglobin reached 80 per cent and the erythrocytes 3,770,000, fourteen months after operation, but a relapse occurred two years after operation, at which time the hemoglobin was 36 per cent, and the erythrocytes 2,120,000. Improvement followed this relapse, and the blood is much improved two and one-half years after operation (Table 1).

The Ribierre or fragility test.—The fragility of the red cells in the peripheral circulation to hypotonic salt solution was tested before splenectomy in all but 3 patients, and in 2 of these 3 the clinical characteristics were so clear that there can be practically no doubt of the existence of hemolytic jaundice. The third patient showed an increased fragility when first tested twenty months after operation. In the 15 patients tested, hemolysis was complete at from 0.4 per cent to 0.48 per cent sodium chlorid, with the controls usually at from 0.32 to 0.36 per cent. Results in the individual cases will be seen in Table 2.

TABLE 2.—FRAGILITY TESTS IN HEMOLYTIC JAUNDICE

NON-OPERATIVE AND PRE-OPERATIVE CASES

CASE No.	PERCENTAGE OF SODIUM CHLORID IN WHICH HEMOLYSIS WAS COMPLETE	
	Patient	Control
2 (86218)	0.467	0.425
4 (135948)	0.4	0.34
5 (141268)	0.4	0.34
6 (142074)	0.42	0.38
8 (153245)	0.469	0.389
9 (148209)	0.4	0.36
10 (161538)	0.44	0.38
11 (162670)	0.4	0.36
12 (94675)	0.44	0.38
13 (91298)	0.4	0.316
14 (153653)	0.42	0.36
15 (157525)	0.42	0.36
16 (169405)	0.42	0.38
17 (172287)	0.42	0.36

There was no decided or constant decrease of fragility in the cases after splenectomy. Eight patients were tested at periods varying from fifteen days to one year and nine months following operation. Only two of these showed a normal resistance; in one it was merely temporary. In none was there an increase of resistance. Table 3 shows representative readings.

The finding of an increased fragility of the red cells in members of the patient's family is significant. In one instance the patient's brother, who also had had very mild attacks of jaundice, showed a definite increase of fragility. In another instance the patient's mother, who never had had symptoms which were in the least suggestive of hemolytic jaundice, showed complete hemolysis in 0.4 per cent sodium chlorid. The age of both of these patients at the onset of symptoms was eighteen

years, suggesting that there is probably a congenital factor in some of
the patients who have not had symptoms during childhood.   Therefore,
testing members of families, though there is no familial history of jaun-
dice, becomes of the utmost importance.

TABLE 3.—FRAGILITY TESTS IN HEMOLYTIC JAUNDICE AFTER SPLEN-
ECTOMY

| Case No. | Percentage of Sodium Chlorid in Which Hemolysis was Complete | | Time After Operation |
	Patient	Control	
3 (112836)	0.4	0.34	1 year, 8 months
	0.48	0.36	1 year, 9 months
5 (141268)	0.46	0.36	18 days
6 (142074)	0.42	0.38	15 days
8 (153245)	0.429	0.349	1 month
9 (148209)	0.36	0.36	23 days
	0.40	0.36	4 months
10 (161538)	0.40	0.34	21 days
11 (162670)	0.42	0.32	22 days
	0.4	0.36	2 months
12 (94675)	0.32	0.32	1 month

Urine.—Urobilin and urobilinogen were both present in the five
cases in which the urine was tested for these substances.   Bile was ab-
sent in all cases save one, in spite of the frequency of cholelithiasis as a
complication.   The diagnosis of hemolytic jaundice may be at times
confused by the presence of bile in the urine when an obstructive jaun-
dice has been superimposed upon an acholuric jaundice.

Hemorrhage.—Hematemesis and melena occurred in one instance.
Epistaxis occurred in 4 of the 17 patients, but was never severe.   The
coagulation time (Bogg's coagulometer) was not increased in these
patients with hemorrhage.

Wassermann tests.—The Wassermann tests were negative in 11 of 13
patients tested.   One patient (Case 15) was said to have had positive
Wassermann tests twelve months and five months previous to examina-
tion, and a Wassermann test was positive at the time of examination.
There was also a history of probable infection.   This case was non-
operative.   One brother of the patient had a history suggestive of hemo-
lytic jaundice.   In another patient (Case 6) two Wassermann tests were
positive before operation and one was negative after operation.   A very
careful search of the history and findings failed to reveal any evidence of
infection.   There was no evidence of syphilis in the spleen removed at

operation. It is conceivable that syphilis might produce a condition simulating hemolytic jaundice, though I have been unable to find record of cases in which the characteristics were identical. Case 15, however, may be an example of this occurrence.

Blood-pressure.—A noticeably low blood-pressure was present in all of the cases except one, the systolic frequently reading below 115. The diastolic blood-pressures were consistently low, averaging 72 in 16 cases. This hypotension occurred irrespective of the degree or absence of anemia.

Loss of weight.—In general, very little loss of weight was noted. One patient with a severe form of the acquired type of the disease, however, had lost 48 pounds.

Gallbladder disease.—Three of the 12 splenectomized patients in this series had been operated on formerly for gallbladder disease, probably with the expectation of curing the condition. The incidence of gallstones in the severe types of hemolytic jaundice is high, however. Seven of our 12 operative cases (58 per cent) showed gallstones for which a later operation was usually done. Removal of the gallstones in a case of hemolytic jaundice does not cure the condition, but, on the other hand, a patient after splenectomy may improve remarkably although retaining his gallstones. The formation of gallstones is doubtless an important incident in the course of hemolytic jaundice. The attacks of acholuric crisis become more severe over a period of years and pain is added to the early syndrome of deepening jaundice, abdominal distress, fever, malaise, and headache until the pain becomes the prominent symptom and the attacks are quite typical of cholelithiasis.

The values for hemoglobin-derived pigments in the duodenal content (Schneider test).—The values for urobilin and urobilinogen in the duodenal contents are doubtless an index of the blood destruction present at a given time. There is probably a marked variation in these values according to fluctuations in the course of the disease. They are, however, quite constantly high. Twelve duodenal tests were done on six of these patients. The average in patients before splenectomy was 2050 units for urobilin and 1100 units for urobilinogen. It is probable that in a larger series the values would average higher, for there is clinical evidence of active blood destruction. In two patients with very high values the blood-picture simulated that of pernicious anemia, a greater degree of blood destruction evidently having exhausted the bone-marrow. The same four patients, tested after operation at periods

varying from thirteen days to four months, showed an average of 800 units for urobilin and 625 units for urobilinogen. It will be noted that there is a very considerable decrease in the values after splenectomy and that the decrease of urobilin is proportionately more marked than that of urobilinogen.   The decrease is not as marked in the early period following splenectomy for hemolytic jaundice as it is following splenectomy for pernicious anemia.   The fall in urobilinogen is less marked than in those cases of pernicious anemia in which there is no definite evidence of change in the liver.   Very soon after splenectomy for pernicious anemia urobilinogen falls to zero in 78 per cent of the cases.   The values in one severe case of the acquired type of hemolytic jaundice with a blood-picture of pernicious anemia, obtained only during a relapse one year and eight months after splenectomy, were high, showing a total of 4000 units.   These values were not included in the preceding averages.   This patient had a large liver with probable biliary cirrhosis (Table 4).

TABLE 4.—HEMOLYTIC JAUNDICE

THE VALUES FOR HEMOGLOBIN-DERIVED PIGMENTS IN THE DUODENAL CONTENTS

CASE No.	TIME BEFORE AND AFTER SPLENECTOMY	BILIRUBIN	UROBILIN	UROBILIN-OGEN	TOTAL	REMARKS
3 (112836)	1 year, 8½ months after	+++	3000	1000	4000	Acquired. Estimation during relapse.
8 (153245)	1 day before	+++	4600	1000	5600	Congenital.
	38 days after	Trace	1400	1800	3200	Severe case.
9 (148209)	47 days before	Trace	1400	1000	2400	Familial.
	14 days before	Trace	2000	1200	3200	Mild case.
	13 days after	0	800	1000	1800	
	140 days after	0	Trace	400	400+	
10 (161538)	3 days before	—	500	500	1000	Congenital.
	23 days after	Trace	400	0	400	
11 (162670)	4 days before	+++	1400	1800	3200	Probably congenital.
	21 days after	++	1000	200	1200	
14 (153653)	Non-operative	+	3000	Trace	3000+	Probably familial.

Transfusion.—Preoperative transfusions were not necessary in any of the cases of this series.   One patient who returned one year and eight months after splenectomy in a relapse of anemia improved after two transfusions.

Post-operative course.—The immediate improvement following splenectomy for hemolytic jaundice is very striking. The jaundice frequently becomes noticeably improved within twenty-four hours and may entirely disappear during the first few days.   The condition of the blood likewise rapidly improves.   Our first patient was operated on July 30, 1911, five and one-half years ago, and has been in excellent condition ever since that time.   She had been constantly jaundiced from infancy

to the time of splenectomy and has never been jaundiced since. During the five years preceding splenectomy she had had recurring attacks of anemia but has not been anemic since splenectomy. There was one operative death, a mortality of 8+ per cent. Reports from all save two of the other patients have been uniformly good. One boy of nine years who had an extremely large spleen and an enlarged liver, together with a very severe grade of anemia, has been in robust health since splenectomy. The condition of his blood improved with extreme rapidity after operation without any form of medical treatment other than hygienic care. Fifteen months after splenectomy the patient was in excellent health. The disease in the two patients who have not done so well was of the acquired type. One of them died four months after splenectomy. The other rapidly became very much improved and was in excellent health for one year and a half. She then had a relapse of both the anemia and jaundice, but improved satisfactorily after two transfusions and is now in good health again. The remaining eight · patients have been well for twenty-three months or less (Table 5).

DISCUSSION

Hemolytic jaundice may be regarded as the diagnostic keystone of the diseases associated with splenomegaly and anemia. In clinical significance it may be said to occupy the position of a group of diseases with cirrhoses of the liver, syphilis of the liver with splenomegaly, and obstructive forms of chronic jaundice, on the one hand, and pernicious anemia, splenic anemia, leukemia, and splenic Hodgkin's disease on the other. An appreciation of the characteristics of hemolytic jaundice gives a new insight into the diagnosis of these interesting diseases. The differentiation between chronic jaundice due to obstruction of larger ducts and hemolytic jaundice (which in part may be due to obstruction of smaller ducts) depends largely on a recognition of the type of jaundice present. The jaundice of uncomplicated hemolytic jaundice is an intensified "hemolytic" icterus, an exaggerated form of the icteroid tinge so constantly seen in pernicious anemia. It is an acholuric jaundice; there is no bile in the urine. It is not associated with pruritus. It is of a chronic nature and may be comparatively deep or of mild grade. It is usually remittent in type and never entirely disappears. In obstructive jaundice there is cholic urine and frequently acholic stool; in hemolytic jaundice, acholic urine and cholic stool. The second more important distinction between obstructive jaundice and hemolytic jaundice lies in

TABLE 5.—HEMOLYTIC JAUNDICE—SPLENECTOMY

CONDENSED TABULATION

CASE	SEX AND AGE	FAMILY HISTORY	JAUNDICE	SPLEEN	ACCESSORY SPLEENS	LIVER	GALL-STONES	FRAGILITY (HEMOLYSIS COMPLETE)	HEMOGLOBIN, PER CENT	ERYTHROCYTES, MILLIONS	DATE OF SPLENECTOMY	RESULT	REMARKS
1 (23194)*	F 22	Not familial. Congenital.	Since infancy. Acholuric.	Chronic splenitis. 1550 grams.	1 large (removed).	Enlarged. Moderate cirrhosis.	+	Not tested.	66	2.95	6/30/11	Five and one-half years well, weight and color. Good color. No jaundice.	History clear for hemolytic jaundice. Gallstones removed seven years previously.
2 (36218)	F 35	Acquired.	Two years. Acholuric.	Chronic splenitis. 900 grams.	...	Enlarged. No duct obstruction.	0	0.467	58	3.00	6/30/13	Death four months after operation. Terminal areas of superficial gangrene.	Jaundice never entirely disappeared.
3 (112856)	F 40	Acquired.	Three years. Choluric at times.	Chronic splenitis. 910 grams.	1 not removed.	Greatly enlarged. Smooth.	+	Post-operative .48	35	1.80	8/22/14	One and one-half years good health and color. Two years after operation relapse. Two and one-half years general condition good.	Severe case with blood-picture of a primary anemia. Gallstones removed at time of splenectomy.
4 (155948)	M 19	Not familial. Congenital.	Since infancy. Acholuric.	Chronic splenitis. 1050 grams.	2 small removed.	Enlarged. Not cirrhotic.	+	0.4	79	4.32	7/23/15	Twenty-three months after operation. Excellent general condition. No jaundice.	Gallstones not yet removed.
5 (141268)	M 9	Familial? Congenital.	Since birth. Acholuric.	Chronic splenitis. 1370 grams.	2 (1 removed)	Enlarged.	0	0.4	24	1.34	9/25/15	One year three months after operation excellent health. No jaundice.	...
6 (142074)	M 21	Not familial. Congenital.	Since childhood. Acholuric.	Chronic splenitis. 498 grams.	...	Normal.	0	0.42	50	3.60	10/27/15	One year two months after operation excellent health. No jaundice.	Cholecystotomy elsewhere three years previously. Two positive Wassermanns before operation; one negative after. No history of lues.
7 (148510)	M 24	Not familial. Congenital.	Since infancy. Acholuric.	Chronic splenitis. 1000 grams.	1 removed.	Slightly enlarged.	0	Not tested.	58	3.23	12/31/15	Death one day after operation.	...
8 (153245)	F 38	Familial. Congenital.	Probably since infancy. Acholuric.	Chronic splenitis. 1700 grams.	...	Greatly enlarged.	+	0.469	47	2.84	3/4/16	Nine months after operation hemoglobin 90 per cent. General health satisfactory.	Gallstones removed at secondary operation. Very severe case.

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No.	Sex/Age	Etiology	Duration	Spleen (weight)	Stones removed	Spleen condition					Date	Follow-up	Remarks
9 (148209)	M 20	Familial.	Two years. Acholuric.	Chronic splenitis, 800 grams.	1 removed.	Slightly enlarged and cirrhotic.	0	0.4	80	5.00	5/4/16	Seven months after operation color and general health excellent. Slight jaundice at times.	Cholecystectomy three months previously. Brother showed increased fragility.
10 (161358)	F 27	Congenital.	Since infancy. Acholuric.	Chronic splenitis, 560 grams.	...	Probably normal.	+	0.44	64	3.86	6/10/16	Six months after operation color and general health very good. No jaundice.	Cholelithotomy at time of splenectomy.
11 (162870)	M 31	Familial? Congenital?	Twenty-one years. Acholuric.	Chronic splenitis, 1250 grams.	...	Normal.	+	0.4	67	3.65	6/23/16	Three months after operation color and general health very good. No jaundice.	Gallstones not yet removed.
12 (94675)	F 30	Familial. Congenital?	Twenty-three years. Acholuric.	Chronic splenitis, 1780 grams.	...	Normal.	+	0.44	69	3.34	9/21/16	Two months after operation excellent color and general condition. No jaundice.	Cholecystectomy at secondary operation.

HEMOLYTIC JAUNDICE—NON-OPERATIVE

No.	Sex/Age	Etiology	Duration	Spleen		Spleen condition						Follow-up	Remarks
13 (91298)	M 23	Acquired?	Two years. Acholuric.	Moderately enlarged.	...	Normal on examination.	...	0.4	90	4.76	...	Three and one-half years after examination. General health good. Jaundice persists and recur.	...
14 (158858)	M 23	Familial?	Five years. Acholuric.	Moderately enlarged.	...	Markedly enlarged.	...	0.42	60	3.90	...	Nine months after examination health good. Mild attack of jaundice.	Mother showed increased fragility but had no jaundice.
15 (157325)	M 24	Familial? Acquired?	Two years. Acholuric.	Moderately enlarged.	...	Normal on examination.	...	0.42	80	4.92	...	One year after examination. Has had one severe crisis with jaundice. Two negative Wassermann tests.	History of lues. Wassermann positive. May be luetic splenomegaly. Brother had history suggestive of hemolytic jaundice.
16 (169403)	M 31	Familial? Congenital.	Since childhood. Acholuric.	Slightly enlarged.	...	Slightly enlarged.	...	0.42	84	4.80	...	Six months after examination, good health.	History of father and one sister suggestive of hemolytic jaundice.
17 (172287)	M 15	Familial?	Since infancy. Acholuric.	Palpable.	...	Normal on examination.	...	0.42	83	5.06	...	Three months after examination general condition good. Color improved.	Mother's fragility increased. Mild, questionable case.

* Case 28194 was reported as one with the clinical syndrome of splenic anemia in American Journal of Medical Sciences, 1913, cxlv, 781–795. Additional history obtained since that time was conclusive for a diagnosis of hemolytic jaundice.

the difference in the resistance of the erythrocytes in the peripheral circulation to hypotonic salt solution. In obstructive jaundice the resistance of the red cells is quite constantly increased—sometimes very markedly increased—while in hemolytic jaundice it is decreased; that is, the cells are more fragile. This has been found to be a congenital condition, and members of the family should be tested for fragile corpuscles in order to obtain exact data concerning the congenital factor in a larger percentage of the cases. An increase of fragility in other members of the family may prove to be corroborative evidence to a diagnosis.

Certain types of cirrhosis of the liver with jaundice may prove to be impossible of a clinical classification. While the spleen is usually smaller in cirrhosis of the liver than in hemolytic jaundice, and the resistance of the red cells is increased, both of these criteria may be vitiated; that is, the spleen may be quite large and the presence of toxic substances and bile-pigments may affect the resistance of the red cells. I have seen so confused a condition in the same patient as cirrhosis of the liver, marked splenomegaly, cholelithiasis, and a pernicious anemia type of blood-picture, when only a definitely increased fragility of the red cells indicated the way to a diagnosis of hemolytic jaundice as the probable primary condition. A more baffling confusion may exist when hemolytic jaundice has progressed through its attacks of acholuric crises to typical attacks of cholelithiasis with a secondary obstructive jaundice superimposed upon the original hemolytic jaundice. In this event, the Ribierre test for an increased fragility of the erythrocytes, if positive, becomes of especial importance. Increased fragility, a history of former recurrent attacks of jaundice and crises, together with a predominating splenomegaly and a more or less severe anemia, will usually, upon careful analysis, serve to indicate the proper diagnosis.

Syphilis of the spleen may simulate the clinical picture of any of the other forms of the splenomegalic syndrome. An enormous spleen, deep chronic jaundice, recurrent jaundice, cirrhosis of the liver, and probably even the pernicious anemia type of blood-picture, have each been observed as associated with and probably a result of syphilis. I do not know of an instance, however, in which the exact syndrome of hemolytic jaundice, complete in all its details, has been reproduced by syphilis.

The importance of obtaining a history of recurrent attacks of jaundice is exemplified in the mistake, not uncommonly made, of confusing hemolytic jaundice with simple splenic anemia. The history of every patient with suspected splenic anemia should be reviewed carefully for

former attacks of jaundice and crises of the acholuric type. In this way only will patients with little or no jaundice at the time of examination be differentiated. Hemolytic jaundice is always to be considered before a diagnosis of splenic anemia is made.

Pernicious anemia may simulate hemolytic jaundice. Given a young patient with a large spleen and evidence of very active hemolysis resulting in a moderate degree of icterus, hemolytic jaundice would at once be suspected. The pernicious-anemia type of blood-picture with high color index occasionally occurs in hemolytic jaundice when myelotoxic. features have developed, and this finding further confuses the picture. It would appear that the chief reliance in these cases must be placed upon the absence of a typical history of pernicious anemia and the finding of fragile red cells; for in pernicious anemia there is not the increased fragility which is found in hemolytic jaundice. In many of our cases of pernicious anemia in which the Ribierre test has been done the resistance of the erythrocytes to hypotonic salt solution has been constantly normal or increased.

Splenic Hodgkin's disease usually remains undiagnosed until surgical exploration or autopsy. The spleen may be nodular, and this characteristic is possible of recognition upon physical examination. A history of the former enlargement of the lymph-nodes may be obtained although the lymph-glands may be small and the spleen large at the time of examination. In every case of splenomegaly the condition of the lymphatic system demands observation, and if necessary, a gland should be excised for pathologic diagnosis. I have recently seen two patients with Hodgkin's disease who presented very large spleens and small lymphatic glands; in one of these a diagnosis was made upon the microscopic examination of an excised gland.

Leukemia may be seen during a period when the spleen is only moderately enlarged, the anemia is severe, a blood-picture simulating the primary type of anemia is present, and myelocytes are absent. With any considerable enlargement of the spleen in leukemia, however, the blood-picture is usually, though not always, pathognomonic. One patient came under my observation in whom a characteristic blood-picture of leukemia was not obtained until several years after splenectomy. The case had been formerly regarded as one of splenic anemia. In a more recent case of leukemia there was some resemblance to hemolytic jaundice, but the fragility of the erythrocytes was not increased.

A very valuable general discussion concerning the diseases asso-

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ciated with splenomegaly, anemia, and jaundice has been published by
Krumbhaar. The literature of splenectomy in the treatment of hemo-
lytic jaundice was summarized in 1915 by Elliott and Kanavel who were
able to collect 48 cases. Their earliest case was operated on by Sir
Spencer Wells in 1887, and reported by Dawson twenty-seven years
later as cured. The fragility of the erythrocytes in this case was still
increased. A patient operated on by Bland Sutton in 1895 was well
ten years later. Since the publication of the report by Elliott and
Kanavel, Hellstroem has recorded two cases, Peck three, and Friedman
and Katz one. Including the twelve cases here discussed, a total of
sixty-six cases of splenectomy for hemolytic jaundice has been reported.
The surgical indications and technic of splenectomy have been elaborated
by Mayo and Balfour.

SUMMARY

1. Seventeen cases of hemolytic jaundice are reviewed, of which
four are probably of the acquired type. In twelve of them splenectomy
was performed.

2. An increased fragility of the erythrocytes in the peripheral circu-
lation was a constant finding in all the 15 patients tested. This increased
fragility was found to persist at varying periods after splenectomy in
7 of 8 patients tested.

3. The values for urobilin and urobilinogen in the duodenal contents
were high in 6 patients in whom they were estimated. There was an
appreciable fall in these values following splenectomy.

4. In 7 (58 per cent) of 12 splenectomized patients gallstones were
present. The removal of gallstones has not cured hemolytic jaundice.
On the other hand, patients with hemolytic jaundice who were splen-
ectomized have been cured of their jaundice and anemia though
retaining the gallstones.

5. Of the 12 patients on whom splenectomy was performed, 10 are
living; 9 are in excellent health without jaundice or anemia. There
was 1 operative death. One patient died four months after operation;
another patient with a severe form of the acquired type of the disease
was in excellent health for eighteen months, had a relapse after two
years, and is again in fairly good health after two and one-half years
following two transfusions. Four patients have been in excellent
health for fourteen months, fifteen months, twenty-three months, and
five and one-half years respectively.

REFERENCES

1. Balfour, D. C.: The technique of splenectomy. ·Surg., Gynec. and Obst., 1916, xxiii, 1–6.
2. Elliott, C. A., and Kanavel, A. B.: Splenectomy for hemolytic icterus. Surg., Gynec. and Obst., 1915, xxi, 21–37.
3. Friedman, G. A., and Katz, E.: Report of a case of acquired hemolytic jaundice with splenectomy. Jour. Am. Med. Assn., 1916, lxvii, 1295–1297.
4. Hellstroem, N.: Two operated cases of hemolytic icterus. Tr. XI North. Surg. Cong., Goerteborg, 1916.
5. Krumbhaar, E. B.: Classification and analysis of clinical types of splenomegaly accompanied by anemia. Am. Jour. Med. Sc., 1915, cl, 227–245.
6. Mayo, W. J.: Surgical considerations of splenectomy. Ann. Surg., Phila., 1915, lxii, 172–176.
7. Mayo, W. J.: The spleen: its association with the liver and its relation to certain conditions of the blood. Jour. Am. Med. Assn., 1916, lxvi, 716–721.
8. Peck, C. H.: Splenectomy for hemolytic jaundice. Jour. Am. Med. Assn., 1916, lxvii, 788–790.
9. Schneider, J. P.: The splenic pathology of pernicious anemia and allied conditions. Arch. Int. Med., 1916, xvii, 32–41.
10. Schneider, J. P.: Further, quantitative study of the duodenal blood-derived pigments. Arch. Int. Med., 1917, xix, 156–162.

OBSERVATIONS ON THE TREATMENT OF MYE-
LOCYTIC LEUKEMIA BY RADIUM*

H. Z. GIFFIN

Renon, Degrais, and their associates (1910) were the first to treat myelocytic leukemia by means of radium exposures over the enlarged spleen. In 1913 they reported five cases. In the first case satisfactory remissions were obtained with five series of exposures over a period of two years. Death occurred two years and two months after the first treatment. In the case of their second patient a satisfactory result was obtained over a period of nine months, with two series of exposures. Death occurred twelve months after the first treatment. Two patients were in good condition six months after their first treatment. The fifth patient had been splenectomized prior to the use of radium, a 2800 gm. spleen having been removed. Following the splenectomy the leukocytes fell to 27,000, but subsequently rose to 143,000. Benzol was used without apparent effect. The asplenic area was then exposed to radium, and this procedure was curiously followed by a reduction of the leukocytes to 21,500. It was not noted by the authors that the reduction may have been a late effect of benzol; it may, on the other hand, have been due to the direct effect of radium on the large amount of blood in the abdominal cavity. Radium was next applied over the thighs, but the leukocytes rose to 81,600. Radium had been applied over the thighs in one other case of this series without favorable result.

Renon and Degrais mentioned that 12 patients had been treated by other French observers with the initiation of favorable remissions.

In the English literature a few cases have been reported in which radium exposures were followed by remissions. Similar results have been obtained by Peabody and by Burnham in this country in a large series of unpublished cases.

In May, 1916, before the Association of American Physicians,

Ordway presented a complete and instructive discussion concerning radium therapy in myelocytic leukemia, and placed on record a detailed study of one of his cases in which a remarkable remission had been brought about by means of radium emanations. In this case the patient had been formerly resistant to both the roentgen ray and benzol. Death occurred, however, fifteen months after the recognition of the disease.

The results of these various observers lead only to the conclusion that it is important to make use of this method of treatment when possible in order to initiate a remission in a disease with so unfavorable a prognosis. Our own experience from May 15, 1916, to April 1, 1917, comprises a series of 30 consecutive cases of myelocytic leukemia which have been treated by means of the surface application of radium element over the spleen.

Method of application.—In some instances in this series we used 50 mg., and in others 100 mg., of the radium element in tubes. The enlarged spleen was mapped out into squares in the manner described by Ordway and the radium exposed over each area for periods of three or four hours. The total length of time for each series of applications varied from twelve to forty-eight hours; usually, however, the time was from twenty-four to thirty-six hours. Patients remained in bed during exposure. In the early cases the protection consisted only of 2 mm. of lead beneath the radium and 2 mm. of lead over the radium. The radium was held in place by means of adhesive plaster. Superficial burns resulted, but they were never serious, and healed without difficulty. As previously pointed out by Ordway, our experiences demonstrated that the skin formerly traumatized by adhesive plaster was especially susceptible to burn. After adding ½ inch of wood beneath the 2 mm. lead screen, we obtained results equally satisfactory with only occasionally a slight burn. The radium may be raised so far from the skin by means of gauze that little result is obtained from the exposures. When a satisfactory response does not occur, we reduce the protection even to the point of burning the patient. Dr. W. J. Tucker, working with me, devised a biscuit-shaped block which has been used routinely for several months. This consists of ½ inch of wood, 2 mm. of lead, ½ inch of wood bored to receive the tubes of radium, and above this 2 mm. of lead and another ½ inch of wood. The block is held in position by means of a simple canvas belt. An endeavor is made to concentrate the fire through the more massive portions of the spleen.

Clinical experience.—For convenience of presentation our 30 cases

have been classified with respect to the size of the spleen at the time of the original examination. The degree of splenic enlargement is denoted by the Scale 1–4. Scale 4 represents a spleen of enormous size, extending beyond the midline and into the right iliac fossa, practically filling the abdomen; Scale 3, a spleen the edge of which extends well to the right of the navel; Scale 2, a spleen extending beyond a point midway between the costal edge and the umbilicus, and Scale 1, a spleen which is easily palpable or which extends only a couple of inches from the costal edge. Spleens having unusual contour or position have been represented by their approximate equivalents in this scale.

There were four patients with spleens in the Scale 1 group (small but easily palpable spleens) (Table 1). The spleen was reduced to approximately normal size in these four patients in from thirty-nine to sixty-one days, after from 2,000 to 6,600 mg. hours of radium given in from two to five series of exposures. The leukocytes in one instance fell from 207,000 to 12,800 in forty days, and in another from 97,000 to 6,600 in thirty-nine days. The general condition and the anemia in all these patients were definitely improved.

TABLE 1.—MYELOCYTIC LEUKEMIA—RADIUM TREATMENT
Spleen—Scale 1 (Slightly Enlarged)

Number	Previous Leukocyte Count	Previous Neut. Myelocyte Percentage	Subsequent Leukocyte Count	Subsequent Neut. Myelocyte Percentage	Reduction in Size of Spleen	Time Between Counts	Mg. Hours	Number of Treatments
173312	12,200	11.0	3,800	1.7	1 to normal	46 days	5400	4
175574	97,600	19.0	6,600	1.0	1 to normal	39 days	3800	2
186558	207,000	27.7	12,800	8.3	1 to normal	40 days	6600	5
169876	96,000	20.7	8,400	2.7	1 to normal	61 days	2000	2

There were 7 patients with spleens in the Scale 2 group (spleens extending nearly or quite to the region and level of the navel) (Table 2). In 3 of the 7 the spleen was reduced to approximately normal size in from fifty to seventy days after from 2,600 to 5,400 mg. hours of radium given in from two to five series of exposures. Two of these patients were discharged at the end of fifty and fifty-four days from the time of the first exposures, their leukocyte counts having fallen from 188,000 to 9,400 and 329,000 to 7,000. They returned in four months and in two months respectively with leukocyte counts of 107,600 and 62,000 and their spleens slightly enlarged. Reduction again occurred to approximately

normal size in twenty and thirty-one days respectively, with, in one instance, one series of exposures, and in the other, three. The patients were in such good general condition that it was thought inadvisable to extend the treatment to the point of reducing the leukocytes to a normal count. As has been stated, 3 of the 7 patients in this group were discharged with approximately normal size spleens. In the remaining 4 the spleens were reduced to Scale 1.

TABLE 2.—MYELOCYTIC LEUKEMIA—RADIUM TREATMENT

Spleen—Scale 2 (Moderately Enlarged)

Number	Previous Leukocyte Count	Previous Neut. Myelocyte Percentage	Subsequent Leukocyte Count	Subsequent Neut. Myelocyte Percentage	Reduction in Size of Spleen	Time Between Counts	Mg. Hours	Number of Treatments
160937	188,000	28.0	9,400	0.0	2 to normal	50 days	2600	2
	107,600	18.7	68,000	18.3	1 to normal	20 days	800	1
159989	329,000	29.7	7,000	2.3	2 to normal	54 days	4300	2
	62,000	14.3	15,800	3.3	1 to normal	31 days	4450	3
181494	125,600	7.3	3,800	0.3	2 to normal	70 days	5400	5
183015	229,000	19.0	81,800	11.3	2 to 1	21 days	5350	4
187921	8,200	4.7	6,200	1.7	2 to 1	11 days	3600	2
172156	389,000	47.0	147,000	33.3	2 to 1+	13 days	2000	2
	343,000	25.3	42,600	9.3	2 to 1	23 days	7000	4
173445	214,000	29.0	22,000	8.0	2 to 1+	48 days	5400	3

In one case (187921) the diagnosis was somewhat doubtful. The history was satisfactory for myelocytic leukemia, but the leukocyte count was in the neighborhood of 8,000 cells, of which 4.7 per cent were myelocytes. It is quite probable, however, that this case will prove itself to be one of myelocytic leukemia.

In another case of this group, one of long standing (172156), the improvement in the general condition was not commensurate with the reduction in the size of the spleen and the leukocyte count.

There were 11 patients with spleens in the Scale 3 group (very large spleens extending well beyond the level of the navel) (Table 3). Four of the 11 spleens were reduced to Scale 1, or were easily palpable in from twenty-two to one hundred twenty-two days, following 5,800 to 9,400 mg. hours in from three to six series of exposures. Six of the 11 spleens were reduced to Scale 2, or extended approximately midway between the costal edge and the navel. In one there was only a slight reduction. This patient, however, was in very poor physical condition and treatment was not continued.

TABLE 3.—MYELOCYTIC LEUKEMIA—RADIUM TREATMENT
Spleen—Scale 3 (Markedly Enlarged)

Number	Previous Leukocyte Count	Previous Neut. Myelocyte Percentage	Subsequent Leukocyte Count	Subsequent Neut. Myelocyte Percentage	Reduction in Size of Spleen	Time Between Counts	Mg. Hours	Number of Treatments
173772	360,000	29.3	5,800	0.7	3 to 1	69 days	8000	5
177183	712,000	39.7	18,200	6.7	3+ to 1	122 days	9400	6
183919	24,300	12.7	16,000	20.3	3 to 1	41 days	5800	5
188262	222,000	22.3	22,000	9.3	3 to 1	22 days	9000	3
170257	389,000	40.3	20,900	21.7	3 to ?	10 days	1800	1
168142	88,000	50.7	34,600	27.3	3 to 2	12 days	3150	2
169360	142,000	40.3	9,800	9.3	3+ to 2	43 days	3600	2
173740	29,000	20.3	15,200	19.3	3+ to 2	7 days	1400	1
173747	8,200	15.7	1,600	2.3	3 to 2	98 days	3400	3
181399	395,000	32.7	19,000	0.0	3 to 2	41 days	7750	8
52388	258,000	32.7	108,000	27.0	3+ to 3	12 days	4450	2

One patient of Scale 3 group (173747) gave a satisfactory history for leukemia, but the leukocyte count was low—8,200 with 15.7 per cent myelocytes. The leukocyte count became reduced, after three series of exposures, to 1,600 cells, of which 2.3 per cent were myelocytes; the size of the spleen was little changed. In the series as a whole an extreme leukopenia, such as occurred in this case, has been guarded against. The patient began to show changes in the mechanism of coagulation, and slight epistaxis occurred. Transfusion was done, and he improved immediately. Three months later he had a definite leukocytosis, which further corroborated the diagnosis. Another patient of this group (169360) showed a marked hemorrhagic tendency at the time of the first examination, that is, epistaxis, hematuria, petechial and purpuric eruptions, and a very toxic condition. After two series of exposures, a total of 3,600 mg. hours, over a period of forty-three days, all hemorrhage ceased, the patient's general condition improved remarkably, the leukocytes were reduced from 142,000 to 9,800, and the spleen was considerably smaller. It has been repeatedly noted following radium treatment that the hemorrhages cease when the condition of the patient becomes improved. A very rapid improvement and reduction of the leukocyte count occurred in one patient (170257) in whom, after one series of exposures, 1,800 mg. hours, the leukocyte count became reduced in ten days from 389,000 to 29,900.

There were 8 patients with spleens in the Scale 4 group (enormous spleens) (Table 4). The most remarkable results were seen in some of the cases of this group. In 4 of the 8 patients the spleen became reduced

from Scale 4 to Scale 1 in from twenty-six to seventy-five days after
from three to six series of exposures, totaling from 4,600 to 10,000 mg.
hours.   In the remaining 4 cases there was a very considerable reduc-
tion in the size of the spleen and in the leukocyte count, in spite of the
fact that two of the patients were in extremis and no results would
ordinarily have been expected from treatment.   In one instance in this
group the leukocyte count was reduced from 918,000 to 19,600 in
thirty-one days after five series of exposures.   In another instance the
leukocyte count was reduced from 773,000 to 25,000 in seventy-five days
after five series of exposures.   In this latter patient the reduction of the
spleen was remarkable.

TABLE 4.—MYELOCYTIC LEUKEMIA—RADIUM TREATMENT
Spleen—Scale 4 (Huge)

Number	Previous Leukocyte Count	Previous Neut. Myelo-cyte Percent-age	Subsequent Leukocyte Count	Subse-quent Neut. Myelo-cyte Percent-age	Reduction in Size of Spleen	Time Between Counts	Mg. Hours	Number of Treatments
175791	918,000	25.7	19,600	13.0	4 to 1	31 days	8,300	5
162899	280,000	28.0	11,600	0.0	4 to 2	57 days	5,300	3
178556	773,000	35.0	25,000	3.7	4 to 1	75 days	7,700	5
180499	604,000	28.3	5,600	0.7	4 to 1	46 days	10,000	6
176684	215,000	16.3	8,200	4.3	4 to 1	26 days	4,600	3
168742	16,400	17.0	4,200	4.3	4 to 2	33 days	4,500	1
175480	470,000	33.3	157,000	10.3	4 to 3	105 days	7,550	7
166824	644,000	43.0	30,400	34.7	4 to 3	99 days	4,350	3

Another patient of this group (168742) presented a satisfactory
history for leukemia, while the leukocyte count was only 16,400, of
which 17 per cent were myelocytes.   It is apparently not of rare occur-
rence to observe in myelocytic leukemia a huge spleen without extreme
leukocytosis, the case being of more chronic type, with longer history;
this type of case is apt to show a less marked remission as the result of
radium treatment.

It is not possible, without extended discussion, to follow in detail
the individual cases of the series; however, the temporary effect of the
treatment by radium exposures has been demonstrated.   The ultimate
results cannot be summarized at this time, but there is no reason to
believe that the effect will be other than temporary.   In 14 of the 30
cases after a marked reduction of the size of the spleen had been brought
about by means of radium, splenectomy was done without operative

mortality. The post-operative course of these cases cannot be satis-factorily discussed at present.

The differential count.—The reduction not only of the absolute number but also of the relative percentage of myelocytes, is most striking after radium treatment. As a less extreme and quite repre-sentative example one instance (168742) may be cited in which the myelocytes fell from 29.7 per cent of 329,000 cells to 2.3 per cent of 7,000 cells, or from approximately 98,000 cells to 140 cells. It has always been possible to find myelocytes in the smears on prolonged search, though they have occasionally been absent on the routine differential count.

The reduction of the number of neutrophilic polynuclears is also striking. The relative percentage remains approximately the same before and after treatment, but the reduction of the absolute poly-nuclear count is very great; for example, in the case previously cited a reduction from 57 per cent of 329,000 cells to 70.7 per cent of 7,000 cells, or from approximately 187,000 cells to 5,000 cells.

Although the relative percentage of small lymphocytes increases after reduction of the leukocyte count, there is nevertheless a reduction of the absolute count to approximately one-tenth of the original number of cells. The relative percentage of large mononuclears increases after treatment, but some of these are without doubt myeloblasts.

Reactions following the use of radium.—The immediate reactions of radium treatment in the series have been infrequent and mild. Large doses have not been used, and in most instances the series of expo-sures has been of short duration. Only once did vomiting occur, and it was not severe. In 6 instances there was more or less complaint of nausea with weakness; in 2 there was headache, and in 1 there was quite a persistent complaint of backache.

Radium is a powerful element, and it is necessary to study carefully the results of treatment in order to avoid overexposure and possible harm. Repeated applications of radium once a week for several weeks may initiate a severe anemia with leukopenia. If the red blood-cells fall below 2,500,000, transfusion should be considered and radium treat-ment temporarily discontinued. When there is reduction of the spleen and reduction of the leukocytes, one's enthusiasm may lead to over-application. As a rule, we have been content to have the leukocytes fall to 20,000 or 15,000 cells. With a definite leukopenia there seems to be much more likelihood of the occurrence of a crisis, with severe

anemia and hemorrhage.   The anemia may then simulate the primary type, with normoblasts and megaloblasts present.   We have noted a temporarily increased fragility of the red blood-cells shortly after radium exposure.   It is also probable that there is a reduction of plate-lets after excessive radium treatment.   We have learned quite definitely the necessity for the timely use of transfusions in connection with radium treatment.   In general, as patients with leukemia approach a serious condition, severe anemia develops.   If this anemia can be combated by means of transfusion, life can frequently be prolonged.

Improvement in the general condition.—The improvement in the gen-eral condition in some instances is nothing short of remarkable, even after one or two series of exposures.   The appetite returns, the toxemia becomes ameliorated, and the strength rapidly increases.   The improve-ment in the general condition does not seem to be the result of a rapid improvement of the anemia, but is probably due to a reduction of the toxemia and leukocytosis and an increase of appetite.   Very marked improvement of the general condition is frequently seen with only slight improvement of the hemoglobin and red-cell count.   A gain in weight results in spite of the rapid reduction in the size of the spleen.   A certain degree of improvement occurred in all the 30 patients treated.   In 26 there was marked improvement, and in 13 of these a very remarkable improvement.

Cases in which the anemia was not improved.—There were 5 pa-tients in whom at one time or another during the course of the radium treatment a definite improvement in the hemoglobin and in the red blood-cells did not occur.   Three of the 5 were in extremely bad condi-tion.   One was so ill that after one treatment radium was discontinued. Another was a severe bleeder, and was very resistent to treatment, although the bleeding finally ceased and general improvement occurred without transfusion.   The third responded fairly well to a first series of exposures, but returned in a few weeks with severe anemia and ascites.   The remaining 2 of the 5 patients with severe anemia were examples of the results of long-continued exposures.   Leukopenia and severe anemia, together with a petechial eruption and epistaxis, de-veloped.   Transfusions were resorted to, and the patients are both now in very good general condition.

Hemorrhage.—The effect of radium exposures on hemorrhage in myelocytic leukemia is important.   It can be stated definitely that hemorrhages have very promptly ceased after improvement has been

initiated by means of radium. Fourteen patients gave a previous history of hemorrhage. In many instances bleeding had followed the extraction of a tooth. Epistaxis was a more common form of spontaneous hemorrhage. Purpura, petechiæ, and melena also occurred. In only two instances did hemorrhage follow radium treatment when it had not occurred previously. In all of the other hemorrhagic cases the hemorrhage ceased after the first, second, or third exposures. One patient who was a very severe bleeder ceased to bleed after two series of exposures. The two patients who bled only after radium treatment had developed a severe anemia and a leukopenia, and hemorrhages were slight—in one instance epistaxis and in the other petechiæ over the legs. Transfusions were immediately resorted to, with satisfactory results.

SUMMARY

1. Thirty consecutive cases of myelocytic leukemia were treated by means of the surface application of radium element over the enlarged spleen. A dosage of 50 and 100 mg. was used. The protection finally adopted was 2 mm. of lead and ½ inch of wood. The splenic area was mapped out into squares after the manner described by Ordway, and the radium was applied over each square for from two to four hours, with a total exposure usually of twenty-four or thirty-six hours. The exposures were repeated every week until a satisfactory remission was obtained.

2. A certain degree of general improvement, together with reduction of the size of the spleen and of the leukocyte count, occurred in every instance, even in the most advanced and toxic cases. Marked temporary improvement occurred in 26 patients and a remarkable improvement in 13. It is impossible satisfactorily to discuss the subsequent histories of these cases at this time.

3. Hemorrhage ceased, as a rule, after one or two series of exposures. In two instances hemorrhage occurred after radium exposures when it had not occurred previous to treatment. In these instances the hemorrhage seemed to be the result of overexposure; an anemia also developed; both the hemorrhage and the anemia were successfully combated by means of transfusion.

4. In 25 patients there was definite improvement of the anemia, concomitant with the improvement of the general condition. The reduction of the number of leukocytes was due chiefly not only to an absolute, but also a striking relative, fall in the myelocytes; there was a

striking fall in the absolute count of polynuclears, while their relative percentage remained approximately the same.   There was also a marked fall in the absolute count of small lymphocytes.

5. Surface exposures of radium over the spleen of myelocytic leukemia usually effect a very rapid reduction of the size of the spleen, a fall of the leukocyte count, improvement in the general condition, and, together with transfusion, constitute at present a most effective measure in the treatment of the disease.

REFERENCES

1. Murphy, J. B., Means, J. H., and Aub, J. C.: The effect of roentgen-ray and radium therapy on the metabolism of a patient with lymphatic leukemia.   Arch. Int. Med., 1917, xix, 890–907.
2. Ordway, T.: Remissions in leukemia produced by radium in cases completely resistant to x-ray and benzol treatment.   Boston Med. and Surg. Jour., 1917, clxxvi, 490–503.
3. Renon, L., Degrais, and Desbouis: Radium thérapie de la leucémic myeloide.   Bull. et mém. Soc. méd. d. hôp. de Par., 1913, xxxvi, 54–66; 649–651.

PULMONARY EMBOLISM*

An Experimental Study

F. C. MANN

Virchow[1] was the first to recognize embolism and to study it experimentally. Cohnheim[2] was the next investigator to consider the subject. Cohn[3] produced a classic work on embolism in which he considered the subject in its broad aspects, both clinically and experimentally. Welch[4] presented the more recent complete review of the subject, and the clinical and pathologic aspects of pulmonary embolism have been discussed by Wilson,[5] who suggested this investigation.

Many experiments by various investigators have been performed on embolism. However, the main purpose of most of the experimenters has been either to determine the location of the emboli or to study the method by which the lung becomes infarcted. Very few have aimed to determine the mechanism producing death.

Deaths due to pulmonary embolism may be divided into three groups:[6] (1) Immediate death occurring when only a small portion of the pulmonary circulation is obstructed. (2) Death caused within a few minutes and due to a complete or almost complete blocking of the pulmonary circulation. (3) Delayed death, the result of an increase by thrombosis of an initial blockage by an embolus of a portion of the pulmonary circulation.

The cause of death in either Group 2 or Group 3 is very evident. The mechanism by which death is produced by an embolus which blocks only a small part of the pulmonary circulation (Group 1) is unknown.

The present investigation was made for the purpose of determining this unknown factor, a purpose I have not been able to accomplish as it has been possible to produce death experimentally only by a more or less complete blocking of the pulmonary circulation. However, a brief report of the experiments may be of value.

All experiments, unless otherwise stated, were performed under ether anesthesia, and the carotid blood-pressure and respiration were recorded. The emboli were sent into the venous circulation through the right femoral vein except in a few experiments in which the left external jugular was used.

The emboli employed were of two kinds. One kind was made of paraffin with a melting-point of about 43 C. It was found that ordinary Christmas candles offered ideal material for these. By using the different colors it was possible to make each embolus distinctive and thus to tell definitely the relationship between the time the embolus was sent into the circulation and the position in which it was found at necropsy. Furthermore, the melting-point of the candle was such that it became soft and would readily mold at body temperature, but did not form droplets.

The other kind of embolus was made from the animal's own blood. The left external jugular vein and the right femoral vein were dissected free for a portion of their course. Blood-vessel clamps were placed on them and the exposed portion of the veins was allowed to become distended with blood. It was then gently crushed with a hemostat, and after this a few cubic centimeters of tissue extract or blood-serum from the same animal were injected into the damaged veins. Under these conditions large clots formed in the vessels very quickly. When the clamps were removed, the clots were swept into the circulation, the process simulating the detachment of a thrombus in a patient.

The general results of all the experiments were the same. It was impossible to produce death or seriously imperil the life of the animal by emboli until the pulmonary circulation was greatly obstructed (Protocol 1). Some emboli passed from the femoral vein to a branch of the pulmonary artery without producing any effect on either blood-pressure or heart-beat. Usually, however, there was a slight drop in the blood-pressure at the instant the embolus passed through the heart. This drop simulated that of a momentary inhibition of the heart. Section of the vagi, however, did not prevent it. In all probability it was due to a passage of the embolus through the pulmonary valves. This was quickly recovered from and the blood-pressure usually maintained a practically uniform level until many emboli had been sent into the circulation. The first noticeable effect of the emboli was an increase in the venous pressure. The abdominal veins stood out prominently, and small veins severed in the operative procedure which did not bleed at

Fig. 158.—Kymograph record of blood-pressure and respiration in Protocol 1. Time in minutes and seconds. Normal blood-pressure, 90 mm. of mercury. Note the drops in the blood-pressure as the emboli pass through the heart. The break in the record covers a space of three minutes. Note the increase in respiratory movements as the blood-pressure falls.

the time of section began to bleed after the passing of a few emboli. Later, blood-pressure decreased—in some experiments suddenly, in others it fell to zero slowly. The sudden drop was usually found to be due to a sudden blocking of the pulmonary artery, while in the gradual drop the emboli had blocked most of the pulmonary branches, and blood-clots had formed around them. Respiration was unaffected until blood-pressure began to decrease. Then it usually increased in both rate and amplitude. The blood-pressure usually reached zero before respiration ceased.

At autopsy in every instance in which death had been produced by the emboli the pulmonary circulation was found to be almost completely obstructed. Depending on the size of the emboli in some experiments, the pulmonary artery or the two branches were blocked; in others the occlusion occurred in the smaller branches. When the blood-pressure had decreased slowly and venous pressure had increased considerably, many of the emboli sent into the circulation toward the end of the experiment were found in the right ventricle or vena cava.

The position assumed by the emboli in the pulmonary system in relation to the time of the injection was fairly uniform. As would be anticipated, the first emboli passed were usually found in the larger branches of the pulmonary artery, and the first two or three emboli were found in the upper branch of the left branch of the pulmonary artery or in the pulmonary branch going to the largest lobe of the right lung. The positions of the rest of the emboli were never uniform.

As it was found impossible to produce sudden death by emboli in normal dogs without almost complete obstruction of the pulmonary
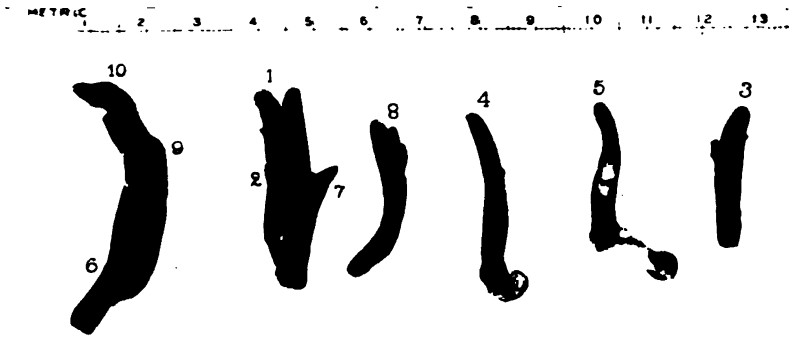
Fig. 159.—Photograph of emboli used in Protocol 1, which were recovered at necropsy.   (Actual size.)

circulation, the procedure was repeated, using animals with a greatly depressed circulation.   In a few experiments the animal was subjected to several hours' anesthesia before the emboli were used;   other dogs were practically moribund with distemper. In all these animals the blood-pressure was low (Protocol 2).   The results in these experiments did not differ from those for which normal dogs were employed.   Death was not produced until obstruction of the pulmonary circulation occurred.

It was deemed possible that general anesthesia was a factor.   To obviate this, in a small series of animals the operative procedures were done under local anesthesia.   The results were the same as when ether was employed (Protocol 3).

In a few experiments the emboli were sent in under sterile conditions. When very many emboli were employed, the animal either died on the

Fig. 160.—Drawing showing the pulmonary artery and branches.   The numbers designate the positions at which the emboli used in Protocol 1 lodged.

table or a short time afterward, or developed infarction of the lungs.   When only a few emboli were employed, the animal was not affected (Protocol 4).

'17—34

Fig. 161.—Kymograph record of blood-pressure and respiration in Protocol 2. Time in minutes and seconds. Normal blood-pressure 60 mm. of mercury. At the signals the clots of the animal's own blood were allowed to enter the circulation. Death was due to a large clot from the right iliac vein which completely blocked the pulmonary artery (Signal 2).

Death from pulmonary embolism usually takes place in relatively strong patients at the time they attempt to leave the sick-room at the beginning of convalescence. They are usually active at the time of death. To simulate this condition a strong animal was fasted for several hours and the emboli passed into the circulation immediately after a period of intense exercise. The results of this experiment were also negative (Protocol 5).

EXPERIMENTAL

Protocol 1.—Mongrel, male; weight 7 kilos.

December 22, 1916, 8.45 A. M.: Animal etherized. The apparatus was arranged to record carotid blood-pressure and respiration. Right femoral vein exposed. Normal record taken, beginning at 9.10 A. M. Emboli of paraffin, 4 cm. in length and 0.5 cm. in diameter, were inserted into the right femoral vein as follows:

TIME	EMBOLUS NO.	COLOR OF EMBOLUS
A. M.		
9.21	1	Lavender.
9.22	2	Blue.
9.22½	3	Red.
9.23	4	Pink.
9.24	5	Yellow.
9.24½	6	Orange.
9.25	7	Green.
9.25½	8	Lavender and yellow.
9.26½	9	Green and yellow.
9.27	10	Red and yellow.
9.28	11	Mixed, several colors.

The blood-pressure was affected as each embolus passed through the heart. Later, blood-pressure began to decrease, the dog dying at 9.47 A. M. Fig. 158 gives the kymograph record of blood-pressure and respiration, and Figs. 159 and 160 give the size and location of emboli.

Protocol 2.—Bulldog, female; weight 18.6 kilos.

December 27, 1916: The animal was in very poor condition. 9.40 A. M.: Etherized. The apparatus was arranged to record blood-pressure

and respiration. A small amount of blood was withdrawn. The right common iliac vein was exposed, as was also the right femoral vein. A blood-vessel clip was placed on the iliac vein, and after the contributory veins were gently crushed with a hemostat, blood-serum taken from the blood which had been withdrawn was injected into the injured veins.
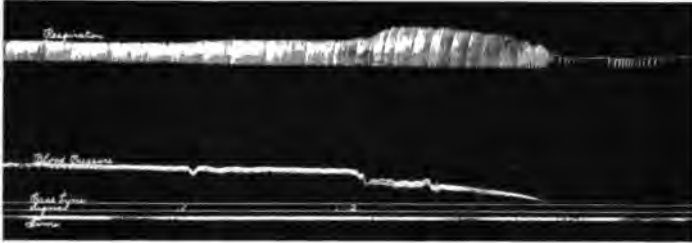
Fig. 162.—Kymograph record of blood-pressure and respiration. Time in minutes and seconds. Normal blood-pressure, 100 mm. of mercury. Each signal marks the passage of an embolus of a blood-clot of the animal's own blood from either the left jugular or the right iliac veins. The clots were made as described in the text. Note the drops in the blood-pressure after the entrance of each embolus. The break in the record covers a space of six minutes. At necropsy both branches of the pulmonary artery were found to be blocked with the clots formed in the veins

The same process was repeated with the left external jugular vein. Clots soon formed in each vessel. 10.37 A. M.: Blood-pressure 60 mm. 10.44 A. M.: The clamp was removed from the jugular vein and the clots were swept into the circulation. The blood-pressure decreased 12 mm. but soon returned to normal. 10.48 A. M.: The clamp was removed from the iliac vein. The blood-pressure immediately fell and gradually
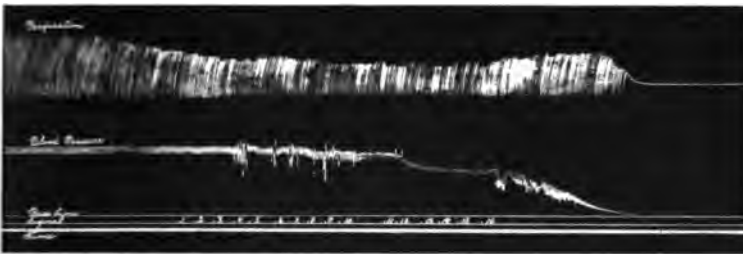
Fig. 163.—Kymograph record of blood-pressure and respiration. Time in minutes and seconds. Normal blood-pressure, 125 mm. of mercury. The vagi were sectioned. The signals mark the time of the insertion of the paraffin emboli (4 by 0.5 cm.) into the right femoral vein. Note that the emboli cause the small drops in the blood-pressure even after section of the vagi. Death was not produced until the pulmonary artery and right ventricle were blocked.

decreased until it reached zero at 10.54 A. M. Fig. 161 gives the kymograph record of the blood-pressure and respiration.

Necropsy was performed immediately. There was a large clot, 3.5 by 1 cm., in the pulmonary artery and extending into the right ventricle. This practically completely obstructed the artery. The left branch of

the pulmonary artery was empty, but most of the terminal branches of the right branch of the artery were blocked with small blood-clots.

Protocol 3.—Collie, female; weight 9.3 kilos.

May 24, 1916: The right femoral vein was exposed under local anesthesia with sterile technic. Ten emboli of paraffin, varying in size from 2.5 to 3.5 cm. long and 0.5 cm. in diameter, were inserted into the vein. The time used in putting the 10 emboli into the circulation was ten minutes. The animal showed no symptoms referable to the emboli. The pulse and respiration remained normal. The animal remained in good condition until May 27, when it developed a marked dyspnea and respiratory grunt. It was bled to death under ether.

Necropsy was performed immediately. The recent femoral wound contained a small hematoma but was not infected. The lungs contained many hemorrhagic areas of infarction measuring 0.5 to 2 cm. in diameter. On the upper anterior surface of the lower right lobe was a small area of marginal emphysema. It was possible to palpate the emboli in the pulmonary artery. There were no emboli in the heart. It was impossible to identify all the emboli as some were broken into two or more pieces. The right branch of the pulmonary artery was completely blocked with the exception of the very small branches. The main branch of the left branch of the artery was completely blocked. The center of each lobe of both lungs was necrotic.

Protocol 4.—Young mongrel, male; weight 9 kilos.

December 14, 1915: The animal was etherized and the right femoral vein exposed, with sterile technic. Four emboli, about 3 cm. long and 0.5 cm. in diameter, were inserted into the vein. The animal recovered quickly from the operation and has been in excellent health up to the present time, fifteen months after operation.

Protocol 5.—Old bulldog, male; weight 8.15 kilos; very pugnacious.

March 27, 1917: The animal had been fasted for eighty hours previous to the beginning of the experiment. About 100 c.c. of blood were removed and set aside to clot. Under local anesthesia the right femoral vein was exposed and clamped with a blood-vessel clamp. After the vein had been traumatized with a hemostat some of the animal's own blood-serum containing small clots was injected. In a short time the vessel was filled with clots. The animal was then exercised for five minutes, after which the clamp was removed from the vessel and the clots were swept into the circulation. The respiration and pulse did not change. The process was repeated with the left external jugular vein. These results were also negative. 1 hour later the animal was etherized and bled to death.

Necropsy was performed immediately. Many of the terminal arteries in every lobe of the lungs were filled with clots. It was estimated that about half of the pulmonary circulation had been occluded.

Figs. 162 and 163 are kymograph records obtained in two similar experiments.

SUMMARY

Emboli made of paraffin and the animal's own blood were sent into the venous circulation of dogs. Death did not occur until the pulmonary circulation was practically occluded. The results were the same whether the blood-pressure of the animal was normal or depressed by ether or disease and whether the procedure was carried out under ether or local anesthesia.

REFERENCES

1. Virchow, R. L. K.: Ueber die Verstopfung der Lungenarterie, Notizen Gebiete Na-
     tur.- u. Heilk., 1846, xxxvii, 26–31.
2. Cohnheim, J.: Untersuchungen über die embolischen Processe, Berlin, 1872.
3. Cohn, B.: Klinik der embolischen Gefässkrankheiten, mit besonderer Rücksicht auf
     die ärztliche Praxis, Berlin, 1860.
4. Welch, W. H.: Thrombosis and embolism, in Allbutt's System of medicine, London,
     1899, vi, 155–285.
5. Wilson, L. B.: Fatal post-operative embolism, Ann. Surg., 1912, lvi, 809–817.
6. Schumacher, Quoted by Meyer, W.: The surgery of the pulmonary artery, Tr. Am.
     Surg. Assn., 1913, xxxi, 223–248.

PULMONARY FAT EMBOLISM—A FREQUENT CAUSE OF POST-OPERATIVE SURGICAL SHOCK*

W. W. BISSELL

It is impossible to review the volumes written concerning the etiology of surgical shock without adding another volume to references already well known to surgeons and practitioners generally. A few references here to the literature on fat embolism, however, are quite essential.

Warthin has recorded the effects on the heart and circulation of injections of oil into the heart directly, into the jugular vein, and into a heart compensating for an artificially produced valvular lesion. The injection of oil directly into the right auricle of a dog causes a marked fall in carotid pressure and a marked rise in auricular and jugular pressure. Warthin also states that repeated injections cause large systolic pulsations in the right auricle, steady fall of arterial blood-pressure, and gradual rise of pressure in the jugular vein and right auricle. He does not refer to the similarity between these experimental observations and the clinical observations on the circulatory phenomena of surgical shock.

The fall in arterial pressure and the rise in venous pressure are precisely what we know to be the case in instances of so-called surgical shock; the patient literally bleeds to death into his own veins.

Fischer has investigated the capillary circulation of the lungs with special reference to fat embolism. He notes that more than 60 per cent of oil injected intravenously into a rabbit soon lodges in the lungs. He also calls attention to experiments by Reuter, who, under his direction, injected oil into the arch of the aorta. This fat also was found in the lungs. While the experimental technic was admittedly crude in a quantitative way, Reuter demonstrated that 62 to 68 per cent of oil injected intravenously could be recovered from the lungs, and 45 to 53 per cent of oil injected into the arch of the aorta also came to rest in lung capillaries.

Fischer explains the retention of fat in the lungs by the great dilatability of lung capillaries, the absence of tissue pressure about the vessels, and the negative alveolar pressure about the capillaries. When oil is injected into the aorta, he explains its accumulation in the lungs by the fact that rabbit arterial pressure is 100 to 120 mm. mercury; pulmonary arterial pressure, 9 to 12 mm.; and capillary pressure, 33 mm. The pressure in the greater (arterial) circulation forces the oil through the capillaries into the venous circuit, where pressure in the right ventricle is insufficient to force it through the lung capillaries. He admits his failure to explain fully the rising blood-pressure in the right heart in pulmonary fat embolism. By inflating the lung alveoli with oxygen to a pressure of 20 mm. mercury, Fischer is unable to force pulmonary fat emboli into the greater circulation. He concludes that a large part of the lung circulation can be occluded without seriously threatening life, and that the importance of fat embolism in man may be overestimated; at all events, fat embolism as a cause of death can play a rôle only where the pulmonary infarction is very extensive.

There are other factors to be considered. I have observed astounding amounts of fat in the *venous* blood of persons with broken bones, and it is presumable that in lipemia from any cause the venous blood is rich in fat. This observation would be of lesser importance had not Gauss demonstrated that addition of 10 per cent of olive oil to blood increases its viscosity approximately three times, or expressed in percentages, the addition of 10 per cent of olive oil to normal blood increases its viscosity 200 per cent.* It being known that pulmonary fat embolism, both in man and experimentally in animals, causes a decreased arterial pressure and increased venous pressure even to fatal termination, it is reasonable to presume that a venous blood rich in fat would offer additional resistance to passage through capillaries due to its increased viscosity. Certainly, it cannot be denied that in the lung capillaries, where fat is accumulated as by repeated injections, the viscosity of the blood must be greatly increased.

* PROTOCOL OF EXPERIMENT BY GAUSS

TIME REQUIRED FOR 1 CM. OF FLUID TO PASS THROUGH THE CAPILLARY UNDER CONSTANT PRESSURE OF 70 MM. MERCURY AND CONSTANT TEMPERATURE OF 24.5 C.

	ALONE SECONDS	PLUS OLIVE OIL SECONDS
Salt solution	33	100
Ascitic fluid	45	130
Human blood-serum	57	180
Human blood slightly diluted with citrate solution	160	480

During the past eight months I have observed six instances of fatal post-operative fat embolism in the necropsy service of the Mayo Clinic. Three of these followed breast amputation; one, ventral herniotomy; one, craniotomy for brain tumor; and one, laminectomy for spinal cord tumor.

I record the following three of these deaths because postmortem examination revealed no lesions other than fat embolism which could be interpreted as important in the explanation of the mechanism of death:

CASE 1 (167261).—A hotel clerk, thirty-two years of age, entered the Mayo Clinic July 26, 1916, in the service of Dr. H. S. Plummer. He complained that ever since boyhood he had suffered the inconvenience of a large umbilical hernia. In 1913 he sought relief in an operation, but after two months a hernia occurred in the operation scar. He stated that the hernia was growing larger and gradually becoming more painful and tender.

Physical examination revealed a well-muscled, but very obese man, weighing 222 pounds, with a large post-operative ventral hernia. Aside from the hernia he presented no noteworthy clinical abnormalities. On three successive days the twenty-four-hour output of urine was normal and the specimens, while containing a trace of albumin, contained no casts or cells. Fifteen minutes after subcutaneous injection of phenolsulphonephthalein the dye appeared in the urine, and in two hours the kidneys returned 110 c.c. of urine, there being 47 per cent of phenolsulphonephthalein in the sample. The average systolic blood-pressure for three days was 133 mm. mercury, and the diastolic, 86 mm. The blood contained 7,400 leukocytes and 80 per cent hemoglobin. The temperature was always normal.

August 5, 1916, the operation was performed by Drs. Judd and Masson. A long transverse incision was made across the abdomen, the hernial sac was freed from its surrounding adhesions to the thick layer of subcutaneous fat, and a mass of the great omentum, approximately 15 cm. in diameter, was removed. On account of a wide diastasis of the rectus muscles, the closure of the sac was made very difficult and during this part of the operation the patient became quite cyanotic, sufficiently so to cause the surgeons considerable alarm. The closure was completed, however, and the patient returned to his bed. He improved during the next twelve hours after proctoclysis and hypodermoclysis. The operation was done toward evening. At its close the pulse was of good quality and the rate was 118 per minute. During the course of the next day the cyanosis persisted and was accompanied by considerable dyspnea. This cyanosis and dyspnea partially subsided by the end of the first twenty-four hours and the patient seemed to be on the way to recovery. During the course of the second day, however, the temperature rose gradually to 100.5 F., and late in the

evening the patient developed a mild delirium. The delirium grew more intense, and by the morning of the second day was associated with tremor and wild hallucinations of sight and hearing. The temperature gradually rose to 105 F., and with it the pulse-rate increased to 140 per minute. Death occurred within forty-eight hours of the operation. During the second day the respiratory rate rose rapidly, breathing was attended with great effort, and there were signs of consolidation of the lobes of the lungs posteriorly (Chart 1).

The patient had offered the history that he had been employed as a bartender and up to three months previous to his appearance for treatment had been a moderately heavy user of alcoholics. Had similar clinical observations been made on a person dead of broken bones, it is probable that the clinical diagnosis of fatty embolism would have been made, but with the remote history of alcoholism and physical signs of consolidation of lung lobes associated with a delirium characterized by hallucinations and tremor, the clinical diagnosis of lobar pneumonia and delirium tremens seemed logical.
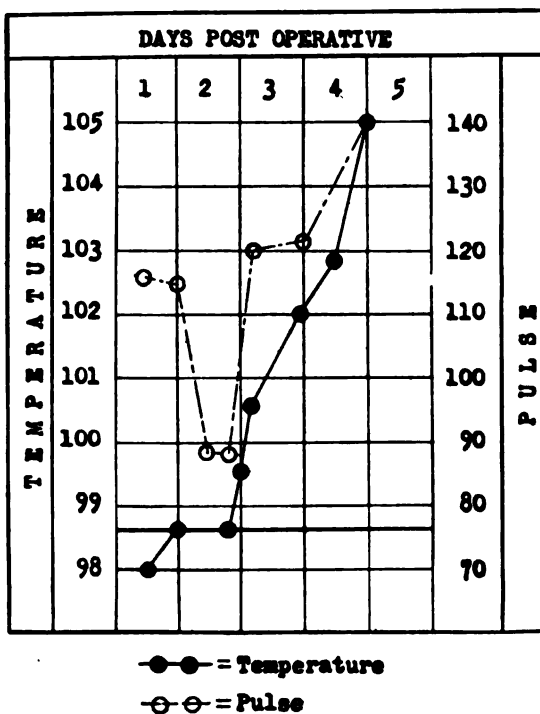
Chart 1.—Temperature and pulse curves after operation. Case 1.

The following necropsy protocol is presented in some detail to impress surgeons more forcibly with the possible extent of post-operative fat embolism:

This is the body of a very obese white man, apparently about thirty-three to thirty-five years of age, weighing well over 200 pounds. Lividity of the face, the neck, the lobes of the ears, and the entire posterior aspect of the body is very marked. Elsewhere the skin of the body possesses the pallor of one dead from hemorrhage. The umbilicus is missing, and at its level there is a recently made laparotomy wound,

28 cm. long, surgically closed with interrupted silkworm-gut retention
sutures and a continuous horsehair skin suture. Body heat is present
in an elevated degree, even externally.
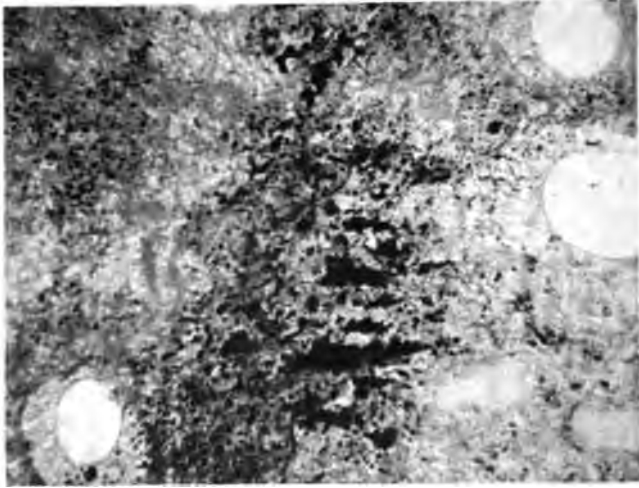
Fig. 2

Fig. 164.
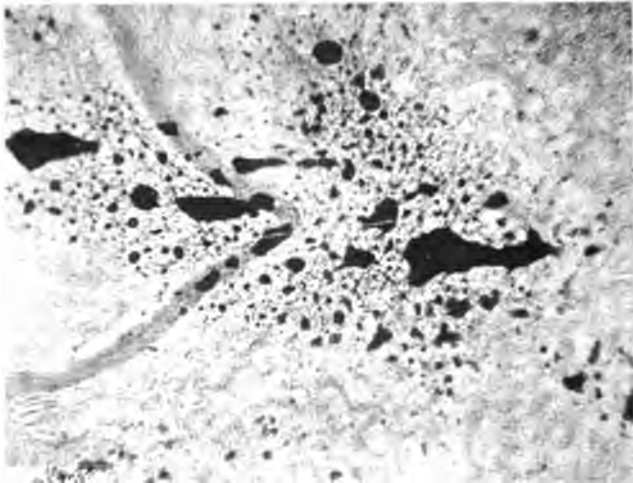
Fig. 1

Scattered over the skin of the abdomen and thorax there are a few
(eleven in all) bright red petechial hemorrhages. These hemorrhages

are approximately equal in size, measuring 1 mm. in diameter. They are to be found only in the skin of the ventral part of the trunk.

On opening the body by the usual midline ventral incision, it is
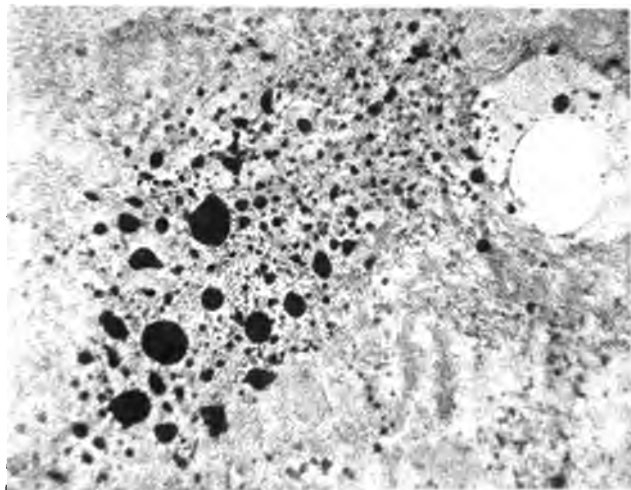
Fig. 4.
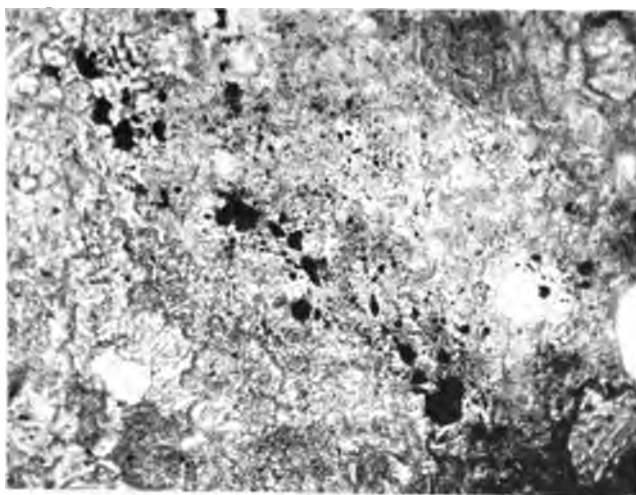
Fig. 3.

Fig. 164.—This illustrates the microscopic distribution of fat in the lungs in the instance of death following umbilical herniotomy. In Fig. 1 fat is seen within the vein as well as in the lung parenchyma. The extensive engorgement of the lungs in a measure explains the clinical diagnosis of lobar pneumonia. Uncounterstained sudan III preparations (× 50).

noticeable that in the depths of the herniotomy wound there is a great deal of fluid fat mixed with a small amount of bloody serum. In the
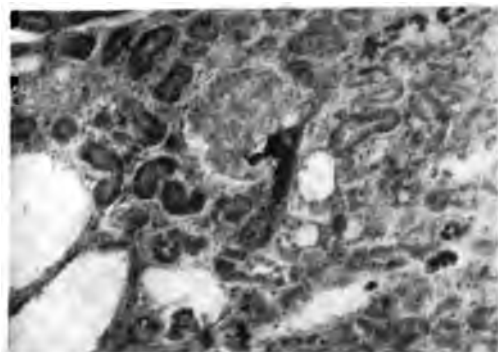
Fig. 1
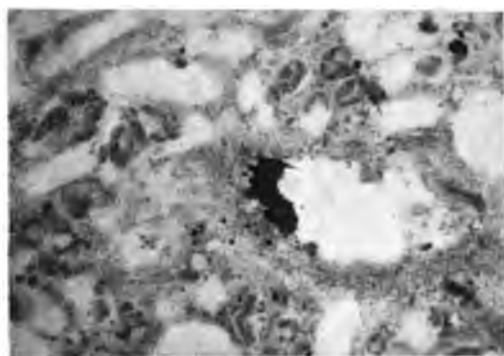
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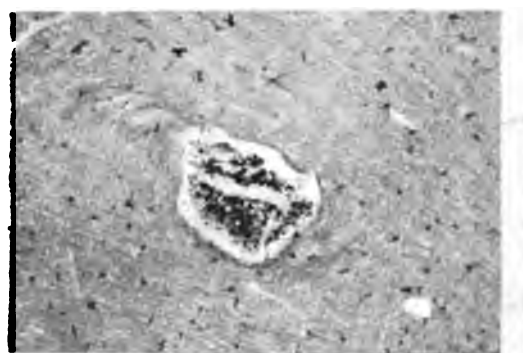
Fig. 3

Fig. 165.
Fig. 165.—Dissemination of fat throughout the body following pulmonary fat infarction illustrated in
4 it is to be remembered that the clinical cause of death included delirium tremens. Sudan III preparations

540
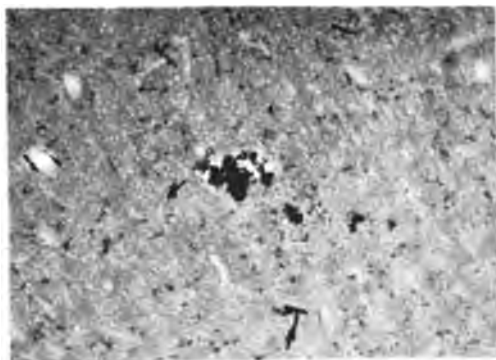
Fig. 4
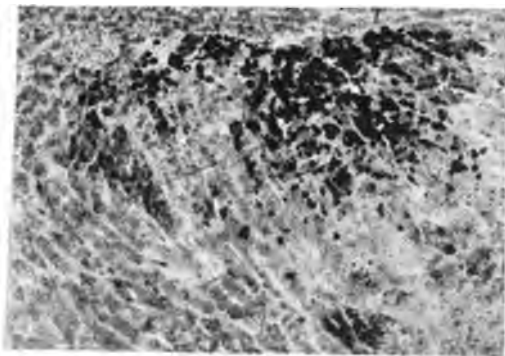
Fig. 5
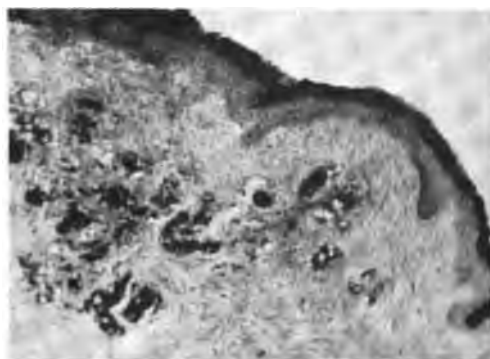
Fig. 6

Fig. 165.
Fig. 1. Figs. 1 and 2 are of kidney, 3 and 4 are of brain, 5 is adrenal gland, and 6, skin.   In considering 3 and
(× 50).

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removal of the hernial sac an elliptic area, 28 cm. long and 20 cm. wide. in the thick subcutaneous fat has been surgically traumatized. The

Fig. 2

Fig. 168
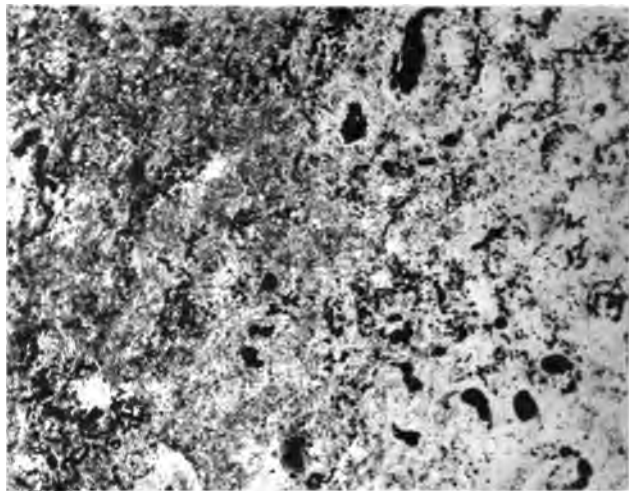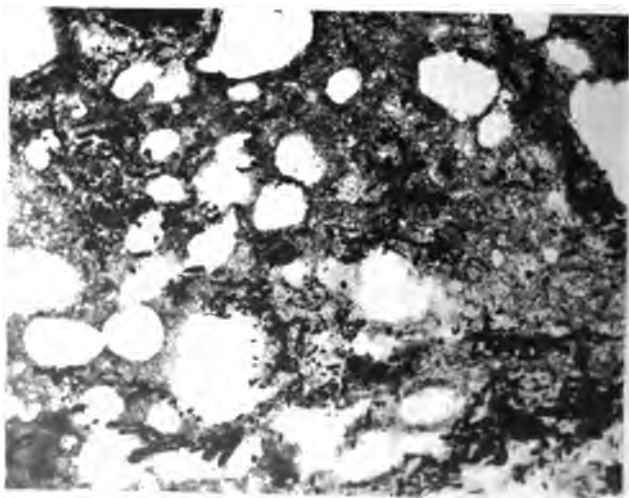
Fig. 1

trauma is apparently minimal considering the size and nature of the operation, and there has been no bleeding. The abdominal fat meas-

ures 10 cm. through its thickest portion. A part of the great omentum has been removed by this operation; the remainder contains an enor-
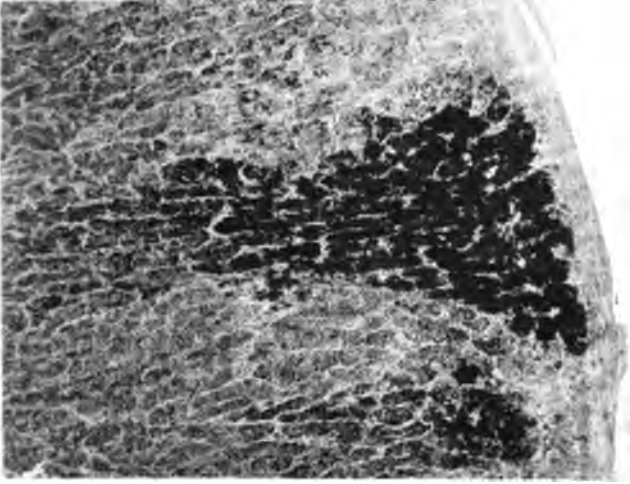
Fig. 4
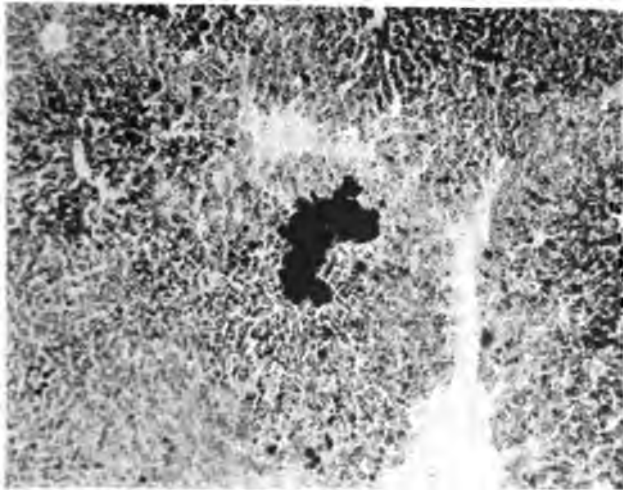
Fig. 3

Fig. 166.

Fig. 166.—Figs. 1 and 2 illustrate extensive pulmonary fat embolism following enucleation of both breasts and cholecystectomy in the second case report. Fat infarction is also observed in the liver and adrenal gland. Sudan III preparations ($\times$ 50).

mous amount of fat. Scattered throughout the visceral and parietal peritoneum are many bright red petechial hemorrhages, the largest of

which measure 3 mm. in diameter. There are no other noteworthy abnormalities in the peritoneum.
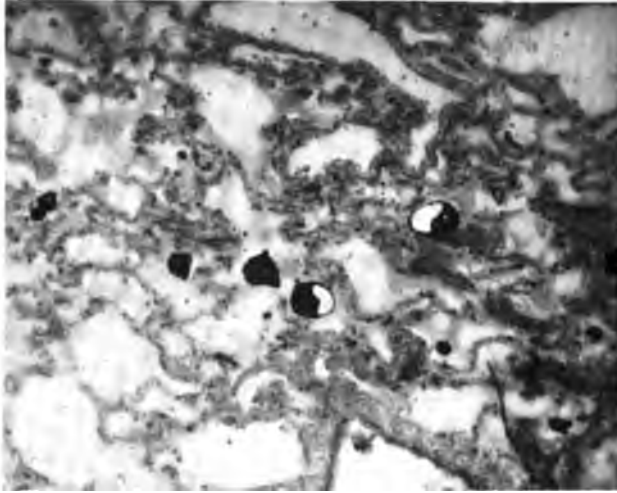
Fig. 2

Fig. 167.
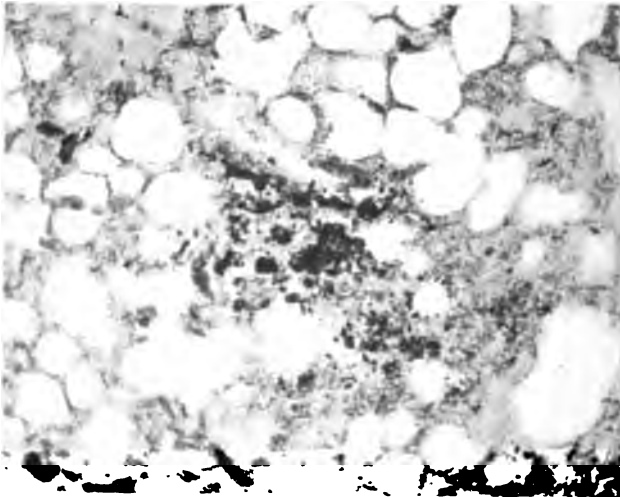
Fig. 1

There is a small persistent thymus in the upper anterior mediastinum. There are no abnormalities in either pleural cavity or in the pericardial

cavity. The great vessels entering the roof of the neck are severed, together with the trachea and esophagus. The entire thoracic content
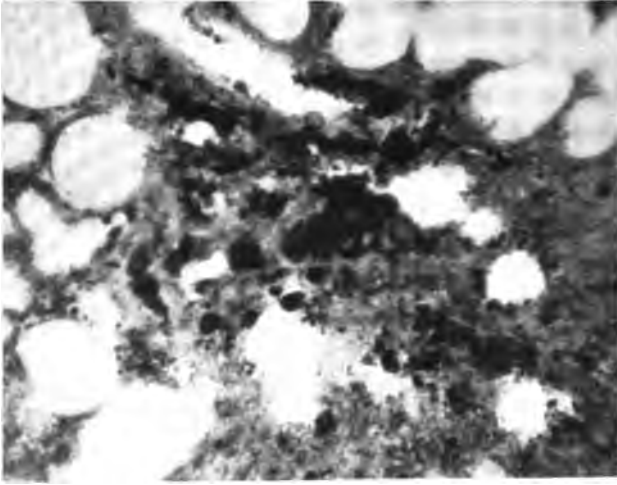
Fig. 4
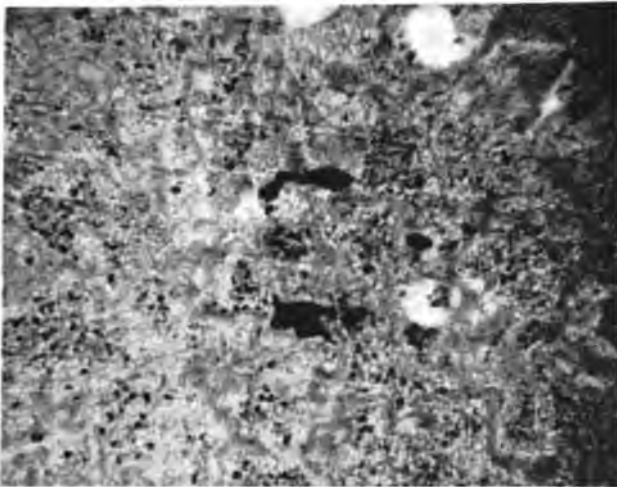
Fig. 3

Fig. 167.

Fig. 167.—The death following Halsted amputation of the left breast was clinically supposed to be due to surgical shock. The dissemination of fat in the lungs is extensive. Marked engorgement of parts of the lung is illustrated in Fig. 3. Sudan III preparations ($\times$ 50).

is reflected downward, the diaphragmatic attachments to the ribs and spine are cut, and the entire trunk is eviscerated except for the contents

'17—35
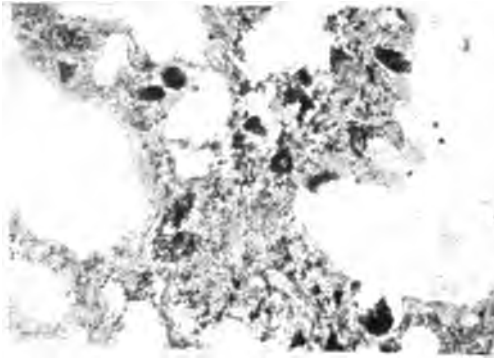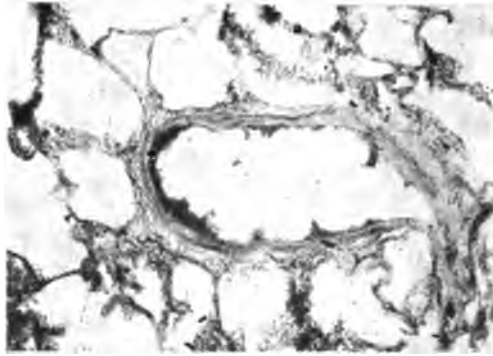
Fig. 1

Fig. 2
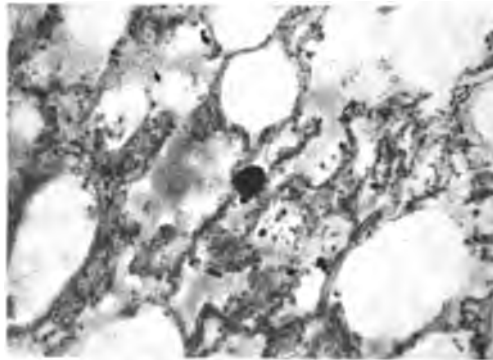
Fig. 3

Fig. 168.
Fig. 168.—Additional evidence of extensive pulmonary fat embolism illustrated in Figs. 1 to 4. Fig. 5
illustrations are of sudan III preparations of tissues removed at necropsy following Halsted breast amputation
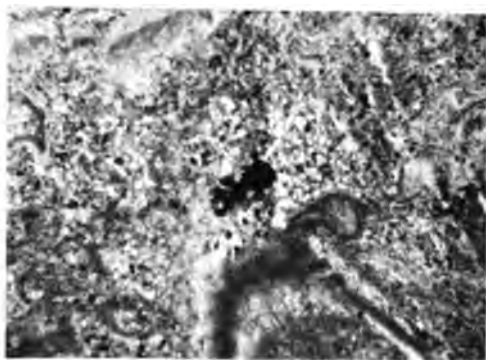
Fig. 4
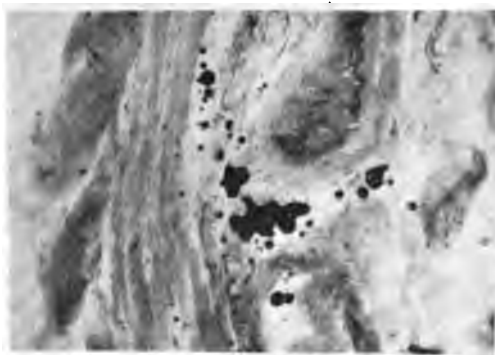
Fig. 5
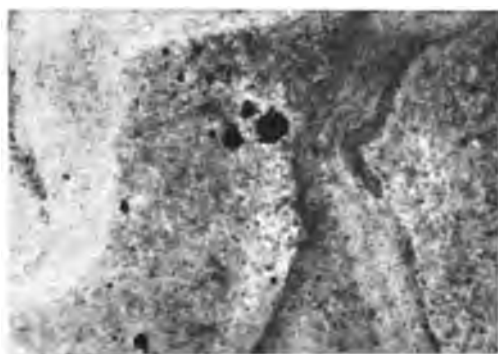
Fig. 6·

Fig. 168.

is a fat infarct in a coil of small bowel.   Fat in the large veins of the spleen is illustrated in Fig. 6.   All these
for cancer (Case 3).

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of the pelvis. By so doing all of the viscera of the trunk can be placed upon a pan across the thighs and examination can then be conducted from behind without removal of organs from their relations to one another, and at the same time thorough examination of the large venous trunks of the body is made possible.

The lungs are quite similar. Scattered throughout the pleura of both are many bright red and faded, dusky-pink petechial hemorrhages. The dependent portions of both lungs are mottled dusky-slate and dusky-pink color. A necropsy pan is thoroughly cleaned with soap and water and dried with clean dry towels. The right lung is carefully washed with running water, and without severing its attachments at the hilum the lower lobe is placed over the freshly cleansed and grease-free pan while the convexity of the lung lobe is cut with a thoroughly cleaned knife-blade. Immediately there is an escape of a great amount of fluid blood, and as this blood runs over the dry surface of the pan, an almost incredible amount of fat in the form of oil droplets is visible floating on the surface. The lungs contain not only a great deal of fluid blood, but also a great quantity of watery, frothy material. The surfaces made by sectioning the lungs are everywhere very hyperemic. Many areas of consolidation are seen in the lung parenchyma as slightly elevated hyperemic areas of finely granular appearance.

The fatty tissues are dissected from the inferior vena cava and the pericardial covering of the auricles. The inferior vena cava is greatly distended with blood and, on incising it, many fat-droplets are visible on the surface of the escaping blood. The blood in the left auricle also contains countless small oil-globules.

Fig. 1

Fig. 169.

Fig. 2

Fig. 3

Fig. 4

Fig. 5

Fig. 6
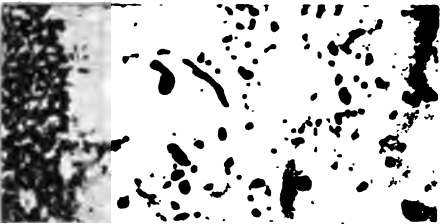
Fig. 7
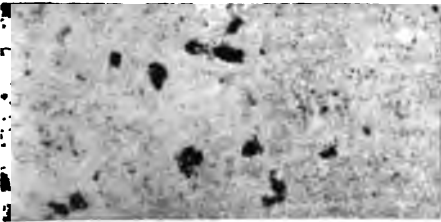
Fig. 8
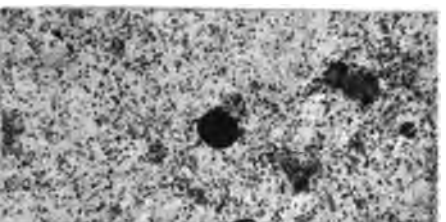
Fig. 9

Fig. 169.

Fig. 169.—This graphically presents a typical experiment designed to artificially produce fatal fat embolism. A young dog weighing 7.4 kilos was placed under ether anesthesia. Apparatus was arranged to simultaneously record the carotid arterial pressure and the pressure in the right auricle. Twenty-three minutes after anesthesia was started 7 c.c. of neutral olive oil was injected into the right femoral vein. One and two minutes later additional fractions of 5 c.c. each were injected. In Fig. 1, the upper light line is the record of venous pressure, the heavy line, arterial pressure, the lower line, time in seconds, and the next lines above, signal and base lines respectively. The intravenous injection of 7 c.c. of oil causes a slight but immediate fall in arterial pressure, with simultaneous rise in venous. The injection of an additional 5 c.c. accentuates these alterations, while increasing the total oil injected to 17 c.c. causes immediate abrupt rise in venous pressure and fall in arterial. After attempted recovery following the third rise and fall of venous and arterial pressure respectively, rapid exodus occurs. The cannulæ were removed from the carotid artery and right auricle immediately on conclusion of the experiment, to make certain the blood-pressures recorded were not caused by clotting. Figs. 2 to 9 inclusive illustrate the dissemination of fat throughout the body; sudan III preparations of lung, kidney, heart muscle, liver, medulla, adrenal gland, pancreas, and right auricle clot in the order named ($\times$ 50).

In any interpretation of this experiment it is to be remembered the animal received approximately two fatal doses of oil.

In the leptomeninges of the brain there is a great deal of watery material and a marked engorgement of all the blood-vessels. The cerebrospinal fluid is greatly increased in amount, but is perfectly clear and watery.

Aside from these descriptions and the lesions named in the anatomic diagnosis, there are no noteworthy gross abnormalities in this body. The contents of the neck and the floor of the mouth are not removed for examination.

Fresh preparations of the top layer of blood running from the surfaces made by sectioning the lung and allowed to stand in a small bottle during the course of the examination contain nearly as many fat droplets as red blood-corpuscles.

Anatomic diagnosis.—Marked obesity; recently made, unhealed and surgically repaired large transverse umbilical herniotomy wound; absence of a part of the great omentum; many oil droplets in the blood contained in the lungs, the inferior vena cava, right and left auricle, right ventricle, and in the large dural sinuses of the brain; disseminated petechial hemorrhages in the skin, peritoneum, and visceral pleura (fat embolism); marked engorgement of all the large venous trunks of the body and the right auricular and ventricular chambers of the heart; marked bilateral pulmonary edema; marked bilateral disseminated bronchopneumonia; marked catarrhal tracheobronchitis; slight hyperplasia of the tracheobronchial lymph-nodes and of the spleen; marked edema of the brain; marked postmortem lividity of the entire dependent portion of the body and of the root of the neck and lobes of the ears; coalescing petechial hemorrhages in the mucous lining of the greater antrum of the stomach, the duodenum, the cecum, and rectum; marked cloudy swelling of the kidneys and myocardium; marked fatty changes in the liver and myocardium; slight varicosity of the superficial veins of the legs.

In the microscopic preparations stained with sudan III fat emboli are found in the lungs, brain, kidneys, liver, heart muscle, spleen, adrenals, and skin. Photographs of some of these microscopic preparations accompany this article.

The purpose of this detailed description of necropsy observations and technic is not only to impress the fact that fat embolism is in some instances a fatal complication in laparotomy, but also to outline a technic for the examination of dead bodies which will demonstrate pulmonary fat embolism if it exists. I realize I am presuming that men who examine dead bodies do not know how to demonstrate fat embolism at the necropsy table. This, of course, is not fair to many pathologists, yet the fact remains that fat embolism is rarely suspected clinically or searched for anatomically unless, perhaps, in instances of persons dying with broken bones.

CASE 2 (170641).—A married woman, forty-one years of age, entered the Mayo Clinic on August 26, 1916, in the service of Dr. W. A. Plummer. There were no details in her family, personal, or menstrual history bearing on her complaint of right upper abdominal, cramp-like pain. She stated that since the birth of her seven-year-old child she had suffered occasional attacks of this abdominal pain which necessitated the use of morphin. The spasms of pain were of sudden onset, usually lasting one-half to two hours, and never followed by jaundice. In all she had suffered five attacks, the last one occurring two weeks previous to this examination. The pains were never associated with eating. They always radiated to the right shoulder-blade. She could not recall that she had had fever with these pains. In addition she called attention to a nodule in the right breast which had been growing since spring.

On physical examination she was found to be a rather stout, little woman, weighing 165 pounds. Her general health was apparently excellent. A palpable nodular and cystic condition was present in both breasts, and there was distinct tenderness over the gallbladder area. There were no axillary enlargements. Examination of the urine revealed nothing abnormal. The blood contained 85 per cent hemoglobin, and the systolic blood-pressure was 130 mm. mercury; diastolic, 78 mm.

Chart 2.—Temperature and pulse curves after operation. Case 2.

Roentgenographic examination of the kidneys, ureters, and bladder did not reveal abnormalities. A clinical diagnosis of bilateral fibrocystic mastitis and cholelithiasis was made.

August 30th, four days after admission, Dr. C. H. Mayo enucleated both breasts by the conservative Warren operation, preserving the skin and nipples. Under the same ether anesthesia he removed a thick-walled gallbladder filled with stones. The entire operation consumed but eighty minutes. Recovery from the anesthetic was normal. Within twenty-four hours the pulse-rate rose to 120 per minute and the

temperature rose from 97.6 F. to 101 F.; some dyspnea and slight cyanosis developed, and the patient became stuporous. During the third day the cyanosis increased and delirium followed. Before death the temperature rose to 103.4 F., and the pulse-rate to 136 per minute. The clinical cause of death was given as surgical shock (Chart 2).

Clinically, this death resembled both surgical shock and fat embolism. The rapid, running, easily obliterated pulse resembled shock. The dyspnea, cyanosis, delirium, and fever resembled fat embolism. Dyspnea, cyanosis, and delirium, however, are noted also in surgical shock.

The necropsy was conducted four and one-half hours postmortem, in the manner outlined in the first case.

Anatomic diagnosis.—Recently made surgically repaired and drained wounds inferolateral to each breast and in the right rectus muscle; absence of both breasts and the gallbladder; moderate obesity; moderate bilateral disseminated fat embolism; fat-droplets in the blood expressed from fresh cuts of lung lobes; fat-droplets in the fluid material in either pleural cavity, in the tracheobronchial secretions, in the urine, and in the blood-clots of the right auricle; disseminated petechial hemorrhages throughout the lining of the small bowel and in the lining of the greater antrum of the stomach; petechial hemorrhages in the mucous lining of the pelvis of the left kidney and in the visceral pleura of both lungs, throughout the peritoneum generally, in the trachea and main bronchi, and disseminated throughout the visceral pericardium and the capsule of the liver; marked fatty changes in the liver; corset deformity of the liver and kidneys; slight bilateral hemohydrothorax; slight amount of fluid and clotted blood in the dependent portions of the peritoneal cavity; remarkable increase in body heat; moderate gas distention of the small bowel; mucohemotracheobronchitis; marked engorgement of all the large veins of the body and of the chambers of the right side of the heart; marked general visceroptosis; atrophic striæ gravidarum of the skin of the abdomen and thighs.

CASE 3 (171631).—The last case report is of a woman fifty-six years of age, entering the Mayo Clinic on September 6, 1916, in the service of Dr. Logan. She complained of a tumor mass in the left breast which had been present for three years, accompanied for two years by a swelling in the left axilla. Her disorder was obviously a carcinoma of the breast with axillary glandular metastases. Physical examination revealed no contraindications to operation. She weighed 160 pounds, which was her normal weight, and there was no evidence of distant metastases of the cancer.

On September 9, 1916, Dr. Beckman removed the left breast and axillary glands by Halsted amputation. The operation consumed seventy-five minutes. The patient recovered from the ether anesthetic very promptly and her pulse was of good quality. Very soon, however, the

pulse rate increased rapidly and the temperature fell below normal. In spite of vigorous stimulation and application of external heat, the temperature continued subnormal and the pulse was very rapid, irregular and difficult to count. There was no evidence of hemorrhage. This condition endured for ten hours before death. The clinical cause of death was given as surgical shock (Chart 3).

At necropsy the following noteworthy gross lesions were observed:

Anatomic diagnosis.—Large, recently made, surgically incised, repaired, and drained wound of the left breast and axilla; absence of the left breast and the left axillary lymph-nodes; slight surgical trauma to the left axillary vein; moderate bilateral disseminated pulmonary fat embolism; moderate bilateral hypostatic hyperemia and edema of the lungs; moderate bilateral hydrothorax; petechial hemorrhages in the mesentery of the small bowel and in the capsule of the spleen; pin-head-sized petechial hemorrhages in the skin; moderate obesity; left apical fibrous adhesive pleuritis; moderate general anemia; marked engorgement of all the large venous trunks of the body; slight chronic diffuse nephritis—slight secondary contraction of the kidneys; marked cloudy swelling of the liver and kidneys; varicosed veins of the legs.

Chart 3.—Post-operation temperature and pulse curves typical of surgical shock.

In considering the two deaths following breast amputations clinically supposed to be due to surgical shock, I would refer the reader to the masterly writings on fat embolism published thirty-three years ago by Dr. Roswell Park. Dr. Park writes as follows:

"During the past winter I was present at an operation for the removal of a cancerous breast from an extremely fleshy woman.

The operation was made by one well qualified to undertake it, and passed off without anything unusual transpiring, except, perhaps, that it was somewhat prolonged. The gland was embedded in adipose tissue, and I noted both that venous oozing was free and that the fatty tissue crumbled readily under the sponge, and even seemed to melt down. The operation was begun about half-past ten. The lady never became completely conscious, and died comatose about five o'clock, with nearly every symptom that I have detailed above.* I am well aware that in this case the trouble may be ascribed to the anesthetic, and with some reason; and yet, all things considered, I hold that the case can be properly classed as fatal from fat embolism. Unfortunately, autopsy, which might have cleared this all up, was denied."

In concluding this article Dr. Park said:

" 1. Fat embolism in varying degrees of severity is not an uncommon complication of surgical accidents and operations.
" 2. *It may be so mild as to be lost sight of in the general condition of shock, or, perhaps, more properly speaking, it is one factor of a condition of prolonged shock.*†
" 3. Our knowledge of the subject will be greatly increased when we appreciate the possibilities of its occurrence and observe our cases more closely, watching for the appearance of fat in the urine, of slight dyspnea, etc.
" 4. When prostration and loss of blood have been great, a moderate amount of embolic disturbance of this kind may serve to turn the scales against a patient who would have otherwise recovered.
" 5. By a proper understanding of this subject certain deaths may be explained which otherwise seem inexplicable.
" 6. Treatment can only be symptomatic, but may accomplish something.
" 7. *Autopsies should be so conducted as to reveal this condition when present.*† "

Among more recent and noteworthy physiologic investigations concerning the influence of vasomotor mechanism in producing a condition of surgical shock, an article by Dr. Mann is most interesting. By experimentation on dogs he concludes:

"The clinical signs of shock which appear after section of the abdomen and exposure of the viscera are due to a loss of circulatory fluid. This loss of fluid is not dependent upon any primary impairment of the

* The symptoms detailed were: Early pallor; somnolence; gradually increasing respiratory rate; increasing dyspnea; weak, rapid, irregular pulse; subnormal temperature at first, but atypical; delirium and coma.
   † Italics are mine.

medullary vasomotor center and takes place at a point beyond the control of the vasomotor mechanism. The causes for this loss of fluid are apparently the same as those which determine the accumulation of fluid in any other irritated area and produce the signs of inflammation. The nervous system probably plays no greater part in the former case than in the latter. The condition is made grave when the viscera are exposed because of the great vascularity of the tissues involved."

Mann's conclusion that the conditions bringing about shock are beyond control of the vasomotor mechanism is indeed gratifying.

Published with this article there are addenda by Bloodgood which concern his critical review of a paper by Mann published a year previously. Bloodgood's criticism is of Mann's statement that it is impossible to reduce the anesthetized animal to a state of shock by any degree of sensory stimulation, providing all hemorrhage is prevented and the abdomen not opened. Bloodgood's criticism is as follows:

"In my experience with operative surgery under general anesthesia in which the condition of the patient has been most carefully recorded and the blood-pressure changes estimated during the entire operation, I have observed extreme degrees of shock in operations other than on the abdomen, even though there had been no hemorrhage; for example, during operation for old, badly united fractures of the shaft of the femur. In these cases the only factors which could have produced shock were the painful stripping of the periosteum and the extreme extension of the limb."

He later adds:

"Among my records there is an anesthetic chart which portrays an extreme degree of shock apparently due to an overdose of ether only; then a second chart recorded during a shoulder-girdle amputation in which there was practically no hemorrhage. The only etiologic factors for the shock were ether anesthesia and trauma."

The reason for citing Park's case is to express the opinion of a leading surgeon of a former time and to compare it with that of a leader in present-day surgery. Had cases been traded about, Park would have had every reason to consider Bloodgood's cases as instances of fat embolism and, on the other hand, Park's case might well have been an instance of surgical shock in Bloodgood's judgment. The real difference in judgment, however, is a fundamental one. The diagnosis of fat embolism, clinically, is based on observations of phenomena produced by distinct, unmistakable lesions grossly demonstrable at necropsy,

while the clinical diagnosis of shock is based on observations of signs and symptoms exactly duplicated in pulmonary fat embolism, but, so far as I am aware, not satisfactorily explained in the examination of dead bodies *unless hemorrhage or pulmonary fat embolism is found.*

The instances of surgical shock cited by Dr. Bloodgood can be classified with pulmonary fat embolism and withstand the test of most severe clinical criticism. It is to be remembered that operations on old ununited fractures and amputations generally are exciting causes of fat embolism.

Since the foregoing has been written Porter has published a note concerning fat embolism as a cause of shock. His third conclusion reads: "Fat in the blood-stream is known not to be injurious per se; its injurious effects are the products of fat embolism."

This conclusion can be contested, at least until we know that the increased viscosity of lipemic blood is not a factor in the retention of large amounts of fat in lung capillaries and in the venous circuit generally. Porter does not distinguish between pulmonary fat embolism and disseminated fat embolism. He offers no explanation of the mechanism of surgical shock as caused by fat embolism.
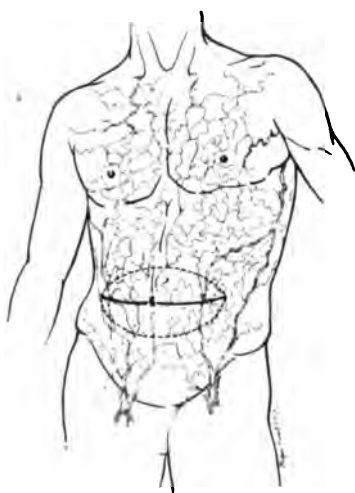
Fig. 170.—Diagrammatic sketch of the larger superficial veins of the trunk anteriorly. The heavy line indicates the incision for umbilical herniotomy. The dotted lines describe an elliptic area of unavoidable surgical trauma in subcutaneous fat rich in large veins.

The exact mechanism of the death, the mode of entrance of fat into the blood-stream, the peculiarities of fat or metabolism, if there are any, which render fat more easily liquefied to enter the blood-stream, the relative proportion of fat in the circulating arterial and venous blood, the viscosity of circulating lipemic blood and the influence of ether anesthesia on pulmonary fat embolism are some of the more important problems to be undertaken to clarify our understanding of this manner of death and to point the way to rational treatment.

However extensive and varied our investigations may be, there are certain very simple and trustworthy clinical data which demand consideration. The frequency of post-operative surgical shock in obese persons as compared to its occurrence in the emaciated or only mod-

erately well nourished is one of these heretofore unexplained, yet unmistakable, clinical observations.

From his wide experience Dr. W. J. Mayo so firmly believes perfect hemostasis to be the positive prophylaxis against surgical shock that he frequently criticizes the now common notions of this clinical complex and insists that with perfect hemostasis there is no shock.

In this connection another simple observation may be cited. In operations in subcutaneous fat, such as the umbilical herniotomy and the

Fig. 171.—Large areas of injury to subcutaneous fatty tissues and veins in operations for conservative enucleation of breasts. Because of omission of undercutting, it is noticeable that few veins are opened by an incised right rectus laparotomy wound.

Fig. 172.—Extensive injury to subcutaneous fatty tissues and veins is caused by radical Halsted amputation of the breast.

breast amputations here reported, it is the common practice for surgeons to ligate the peripheral or bleeding ends of severed veins and leave unligated the central ends which ooze but little blood. With the pressure incident to wound retraction temporary hemostasis is made on the central ends and the possibility of their opening after closure of the wound is overlooked because experience has taught the surgeon that only the peripheral end of these severed subcutaneous veins is likely to bleed. In all of these wounds a pool of blood-serum and oil globules accumulates after wound closure. It seems reasonable to presume

that the gaping mouths of cut veins in such wounds may receive even large quantities of oily material which is conveyed to the lungs through the venous circulation (Figs. 170, 171, and 172).

EXPERIMENTAL

I have repeated the viscosity experiments devised by Gauss and have obtained results entirely similar to his. In addition, it is notice-able that if the dispersion of the oil globules is sufficiently great (the emulsion sufficiently fine), the viscosity of the vehicle is not only not increased, but in some instances the emulsion even seems to be less viscid than the vehicle alone. This is true for normal salt solution, ascites fluid, human blood-serum, and citrated blood.

Many animals have been injected intravenously with neutral olive oil and the effects on circulation recorded. These experiments have been conducted as Warthin conducted them and similar results have been obtained.

It is so obviously true that oil introduced into the venous circulation causes a marked rise in venous pressure and an associated fall in arterial pressure that our attention should now turn to the mechanism of these alterations. It is to be expected that with fall in arterial pressure and rise in venous pressure there is a marked decrease in perfusion rate of the lung. Experiments designed to measure the perfusion rate in lungs infarcted with fat are now in progress.

CONCLUSIONS

1. Deaths clinically supposed to be due to surgical shock are due, in so far as this experience goes, to pulmonary fat embolism and its attendant blood-pressure phenomena.

2. Pulmonary fat embolism causes a lowering of arterial blood-pressure and an elevation of venous blood-pressure which may be sufficient to cause death.

3. Infusions (intravenous) are contraindicated, because of the increased pressure on the right heart.

4. By simple methods pulmonary fat embolism is easily demonstrated at necropsy.

REFERENCES

1. Bissell, W. W.: The amounts of fat in the blood stream of persons with broken bones. Jour. Am. Med. Assn., 1916, lxviii, 1926–1927. Cited by Porter, loc. cit.
2. Fischer, B.: Experimentelle Untersuchungen über die Kapillarkreislauf der Lungen und die Fettembolie. Verhandl. d. deutsch. path. Gesellsch., 1914, xviii, 279–281.

3. Gauss, H.: Studies in cerebral fat embolism with reference to the pathology of coma. Arch. Int. Med., 1916, xviii, 76–102.

4. Mann, F. C.: Shock and hemorrhage: An experimental study. Surg., Gynec. and Obst., 1915, xxi, 430–441.

5. Mann, F. C.: The peripheral origin of surgical shock. Bull. Johns Hopkins Hosp., 1914, xxv, 205–212.

6. Mayo, W. J.: Procedures following nephrectomy. Jour. Am. Med. Assn., 1915, lxiv, 953–957.

7. Park, R.: On fat embolism. N. Y. Med. Jour., 1884, xl, 177–181.

8. Porter, W. F.: Fat embolism a cause of shock. Boston Med. and Surg. Jour., 1917, clxxvi, 248.

9. Warthin, A.: Traumatic lipemia and fatty embolism. Internat. Clin., 1913, iv, 171–227.

SKIN AND VENEREAL DISEASES

'17—36

A CLINICO-PATHOLOGIC STUDY OF AN UNUSUAL CUTANEOUS NEOPLASM COMBINING NÆVUS SYRINGADENOMATOSUS PAPILLIFERUS AND A GRANULOMA*

J. H. STOKES

The case which forms the material for the present study was referred to my service for the diagnosis of a solitary fungous lesion on the inner aspect of the left thigh. The pathologic findings disclosed, to my surprise, a neoplasm the identity of which was only partially suspected from clinical criteria and which was of unusual interest from the standpoint of cutaneous pathology.

REPORT OF A CASE

The patient was an Italian woman, aged twenty-four years, in fair health. General examination disclosed nothing of note other than debility incident to constipation, too frequent pregnancies, and overwork. The woman was hysterical, refractory, and unobserving, and could not be persuaded to remain for a complete study. A rather incomplete history was obtained through an interpreter. Apparently the lesion had been present, in the condition in which it came under our observation, for twelve years, but it had undergone partial regression on several occasions, when kept clean or under medical care. It consisted, as shown in Fig. 173, of two papillomatous, cauliflower-like masses of hypertrophic granulations on the inner anterior aspect of the upper third of the left thigh. It was covered with fetid pus and greenish-yellow crusts, and bled readily on slight trauma, but was not extremely sensitive. Downward and inward from the main mass, which was about 2 cm. wide and about 5 cm. long and 1 cm. high, were several smaller nodules either slightly papillomatous or smooth, rounded, and of a bluish color. Grumous material, blood, and pus could be squeezed from any portion of the condylomatous mass, and this circumstance considerably heightened its resemblance to blastomycosis. The chief clue to the nevoid character of the lesion was found in a patch of linear hypertrichosis extending downward and outward from the smaller of the two vegetating

masses. There were no palpable glands in the groin, and no signs of cutaneous metastasis above the lesions. The patient stated that the bluish nodules at the lower margin of the vegetation had been present for some time, and that the original lesion from which the hypertrophic lesions had developed had been of the same type.

Pending the outcome of biopsy, permanganate wet dressings somewhat reduced the larger mass and controlled some of the infection. A radical excision of the whole mass was then done, including the removal of the inactive (hairy) portion of the nevus. The subcutaneous fat was not involved, and there was no appreciable infiltration of the deeper structures, the lesion being confined to the cutis. At one point a cyst in the deeper portion of one of the nodules was ruptured, discharging a grumous, brownish fluid. Microscopic examination of the pus failed to disclose any traces of blastomyces. The pathologic examination, however, identified it as an apparently benign adenoma of the sweat-glands, on which was superimposed a plasmoma, conforming in many respects to the pathologic picture of pyogenic granuloma and vegetative dermatitis.

PATHOLOGY

The description of the pathology may be divided profitably into two parts—that of the adenoma and that of the granulomatous stroma.

The structure of the adenoma was seen to the best advantage in simple form in one of the smaller bluish nodules. A parakeratotic and sodden epidermis with well-marked acanthosis at the margins of the nodule was pierced by short, parallel ducts, at the mouths of some of which the transition from squamous to cuboid and cylindric epithelium could be observed. The ducts dilated below the orifices, forming bottle-shaped sacs into the lumina of which papilliferous projections had been pushed. There were no signs of abscess formation either in the epidermis or the cutis. In the walls of some of the cystic glands the transition from the epidermal to the glandular type of epithelium was not complete until the deeper portions of the sac were reached, and strands of squamous epithelium formed a retiform network across the smaller spaces, springing evidently from the same groups of cells from which patches of cylindric and cuboid glandular epithelium arose. The cylindric epithelium of the ducts and sacs formed a single, but more often a double, layer of cells, the outer being columnar, the inner cuboid, and resting on a fibrillar structure of connective tissue in the cutis (basement membrane). At no point could any signs of a tendency of glandular cells to leave the basement membrane for the cutis be observed, the structure of the glandular portion adhering strictly to that of an adenoma.

At the margin of one of the smaller lesions a distinct picture of basal-cell extension downward into the cutis was observed in the form of cords and strands slightly suggestive of epitheliomatous proliferation. Cell-rests, oval or irregular in contour, were recognized, forming solid masses,

some of which showed signs of central degeneration or tubular structure. These presumably primitive tubules contained granular material. In close association with them were groups of typical and atypical coil-ducts lined with epithelium, either normal or of various thicknesses. Ducts showing all degrees of cystic dilatation were observed. The cutis in the

Fig. 173.—Vegetative nævus syringadenomatosus of the right thigh. The linea hypertrichosis is visible to the left. Discoloration due to potassium permanganate solution.
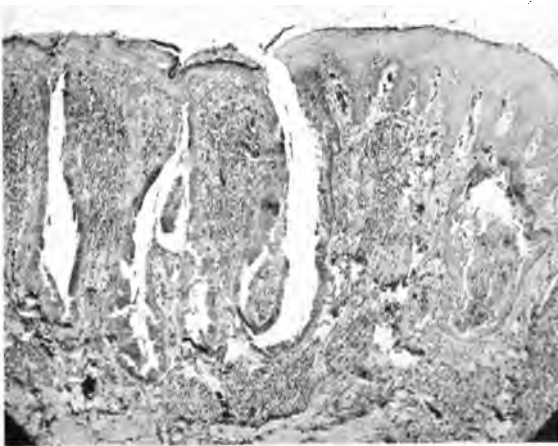
Fig. 174.—Sagittal section of one of the smaller nodules, showing the crypts.

smaller lesions showed signs of a mild inflammatory reaction about the capillary rete, with some invasion of the cutis by lymphocytes and occasional small groups of plasma-cells. A slight increase in the number of mast cells in the small lesions heralded the very great increase observed in the large vegetation. Hyperpigmentation was marked at

the periphery of one of the nodules.

Fig. 175.—Section from the edge of the plasmoma showing cystic and embryonal coil ducts, with transitional stages between solid cords and patent ducts.

Hair and sebaceous glands, as such, seemed to be entirely absent in the nodules and in the main mass, and the structure of the gland-ducts was so obviously of the sudoriparous type as scarcely to admit of doubt as to their identity.

In the large, vegetative lesions the picture described for the smaller nodule was intensified in every particular except that at the margin no sign of a down-growth of basal cells from the epidermis was observed. In the deeper portions of the cutis, beneath the vegetation, however, there were again occasional solid cords of cells scattered among typical and atypical coil-ducts (Figs. 175 and 176). Some of these showed the transitions and cystic degeneration and dilatations, with granular detritus, recognized in the sections of the nodules. Remarkable pictures of papilliferous outgrowths
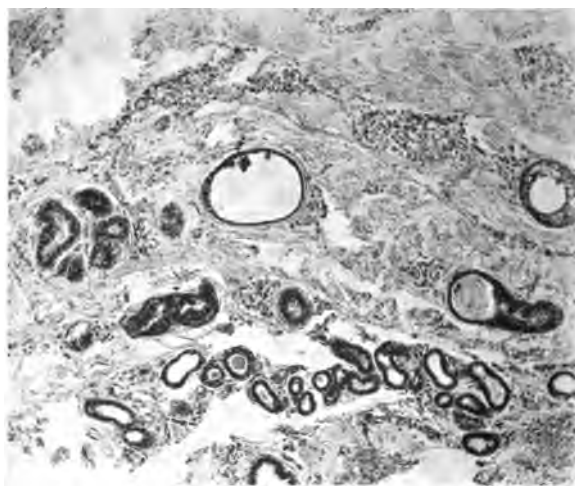
Fig. 176.—Transitions from solid cords to patent ducts.
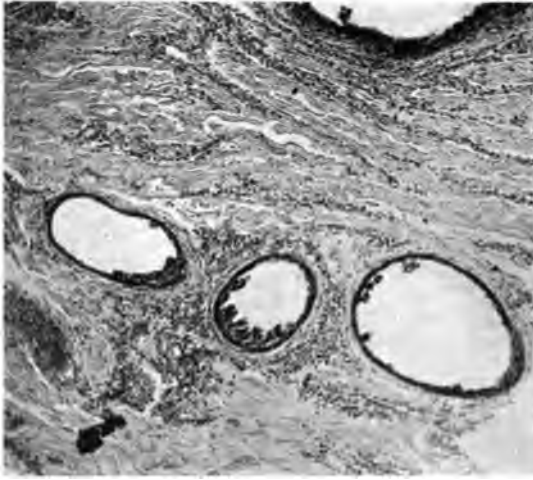
Fig. 177.—Papilliferous projections into the lumina of dilated ducts.

from the single layer of epithelium lining these cystic ducts were observed (Fig. 177).

The metaplasia of epithelium observed in these sections was one of the most interesting features, and well illustrated the varied developmental possibilities of the basal epidermal cell, originating from embryonic ectoderm. At the mouths of the ducts were typical squamous cells, in some cases extending far down into the interior on one side, and on the other being quickly replaced by a single layer of cuboid cells, and again in turn by two layers (Figs. 178 and 179), the inner oblong or cuboid, the outer showing all gradations from short, thick, cylindric to a tall, closely crowded columnar epithelium. Epithelium of this latter type was in places scarcely to be distinguished from that of the trachea, except for its
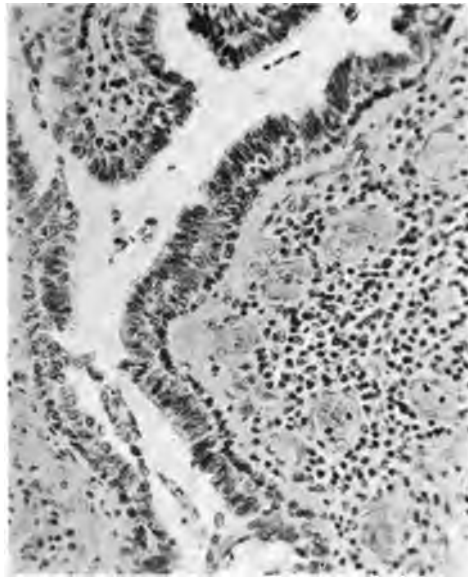
Fig. 178.—Section from large mass. Adenomatous glandular structure; outer layer of epithelium, columnar; inner layer, cuboidal. The vascular structure of the granuloma can be recognized.
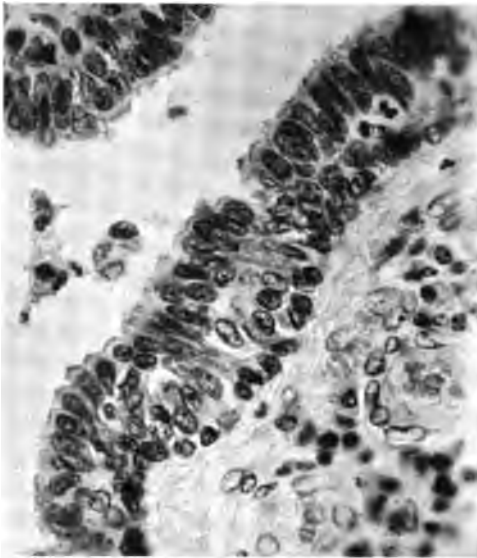
Fig. 179.—Oil immersion showing detail of epithelium. The ciliated appearance is artefact.

lack of cilia. Certain of the groups of tall, cylindric cells, on superficial observation, even seemed to be ciliated, but careful comparison of various parts of· the lesion has convinced me that the appearance is an artefact, due to a deeper staining of the outer edges. Some of the sacculations from the main duct showed trabeculas of rhombohedral cells springing from the same cuboid base as the tall cylindric types. All stages of transition from coil-ducts and solid cords in the deeper portions of the cutis, to the adenomatous sacculations of the upper cutis, could be recognized.

The granuloma responsible for the tremendous vegetative hypertrophy of the larger lesions is of exceptional interest. In the gross, as previously remarked, it suggested a vegetative dermatitis or blastomycosis. In the sections no signs of epithelial abscesses were apparent and the changes in the epidermis as a whole were merely those of a fairly marked acanthosis. No organisms were demonstrable. At the periphery of the vegetating lesions there was considerable lengthening of the rete pegs, but the changes in the corium were slight. Beneath the vegetation the entire upper portion of the corium was transformed into a granuloma, surmounted by a spongy, lobulated mass consisting of innumerable newly

Fig. 180.—Section from a nodule showing cell inclusions and strands in the upper cutis. The epidermis extends to the right from the upper left-hand corner.

formed capillaries and blood sinuses, in a stroma composed of a thin, fibroblastic reticulum, the meshes of which were packed with lympho- cytes, plasma cells, and mast cells, with a few polymorphonuclears and
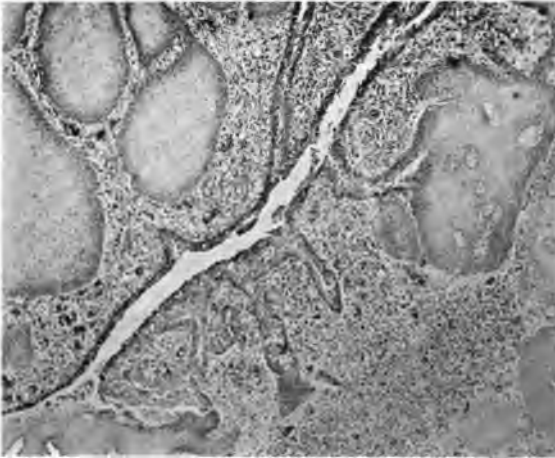
Fig. 181.—Section from the large mass illustrating the close association of glandular with epithelial hyperplasia.
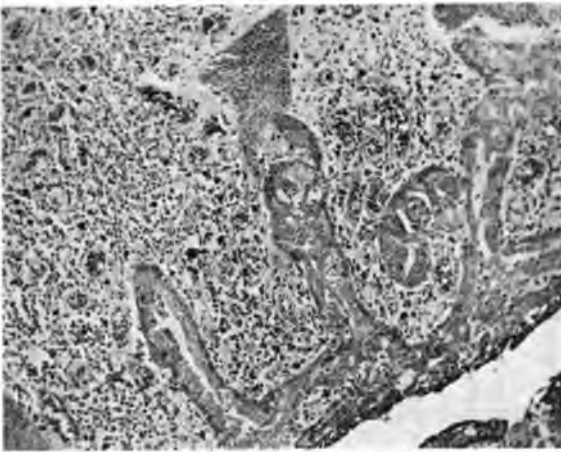
Fig. 182.—Detail of the apparent transition of an epithelial cell inclusion into a glandular structure. The middle duct is not fully formed, and the lumen is filled with transitional types of cells.

eosinophiles. The increase in basophilic cells approximating the mast- cell type is well shown in Fig. 183. Most of these cells were of the smaller, more compact, densely staining type, seen, for example, in the

infiltrations of urticaria pigmentosa in cases in which these cells are present, and in mycosis fungoides.
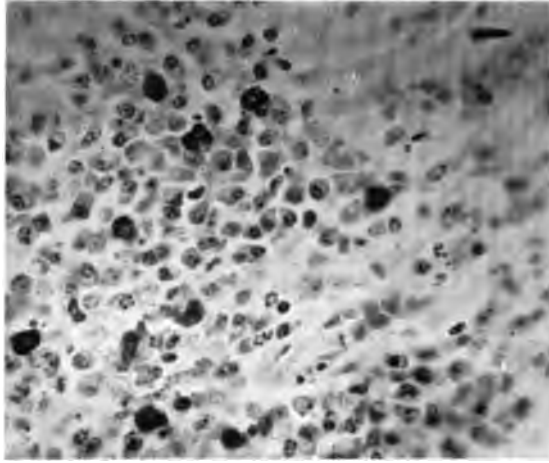
Fig. 183.—Detail of cellular structure of the plasmoma. The large cells are mast cells, lying in a mass of plasma cells, lymphocytes, and fibroblasts.

Fig. 184.—Fibrosis in the granulomatous stroma. Many newly formed blood-vessels.

DISCUSSION

The differential diagnosis of the neoplasm clinically involves the possibilities already mentioned, and could not be regarded as satisfactorily established without microscopic study. No infectious agent other

than pus organisms could be identified. Not only were blastomycetes not found in the tissue, but the pathology also effectually excluded this possibility.

A rich controversial literature has developed about that group of cutaneous neoplasms associated with embryonal rests of epithelium in the cutis which range in type of lesion from basal-celled epithelioma to the benign sudoriparous and sebaceous adenomas. The miliary or disseminated type of syringoma of the conventional text-book description (acanthoma of Unna) has been admirably
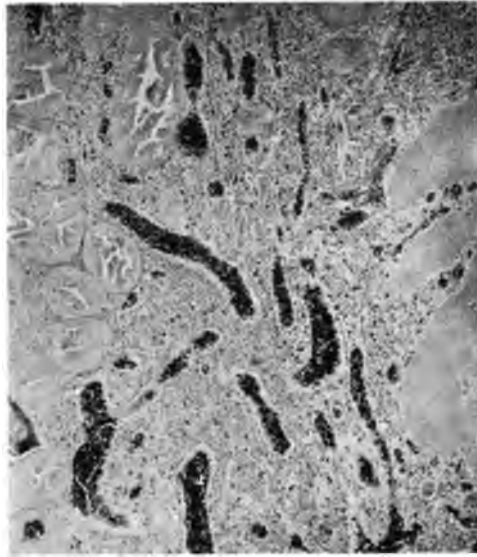
Fig. 185.—Illustrating the vascularity of the stroma.
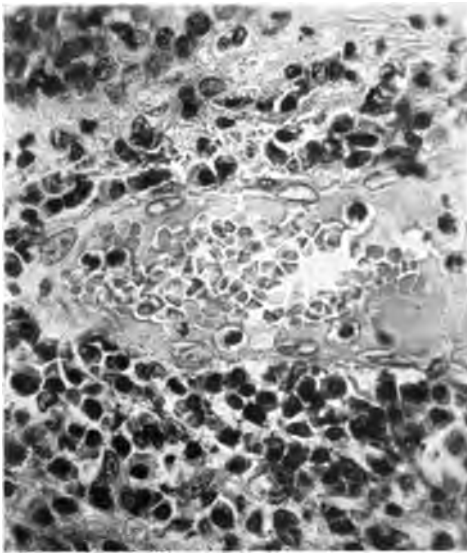
Fig. 186.—Atypical capillary in the stroma. Note the swollen endothelium.

delineated for the American literature by the studies of White, Ormsby, and Sutton and Dennie. The type represented by my case is evidently rare, and the combination with a plasmoma is still more so. In fact, no parallel for this case could be found in the American literature. In the Continental literature the papilliferous adenomatous structure of this nevus has been best exemplified in the cases of Petersen, Wolters, Blaschko, Hedinger, Rothe, and, most recently, in that of Werther. Elliot's case in

the American literature bears some resemblance to mine, but was regarded
by Elliot as an adenoma rather than an adenomatous nevus, though it
developed in association with nævus unius lateris.   It lacks, moreover,
the associated granuloma.   Lesions presenting the combination of nevus
and plasmoma have been observed by Blaschko, Schridde, Boit, von
Weidt (cited by Rothe), and by Hedinger and Rothe on the scalp.
Rothe's discussion of the pathologic findings and their significance is the
most complete.   The solitary syringoma recently reported by Paul
and Adamson is inadequately described and illustrated, so that it is
difficult to base comparisons on it.   The arguments for and against the
nevoid character of these lesions, as distinguished from simple adenoma
of the sweat-glands, are summarized by Sutton.

The case here reported is of peculiar interest in that apparently the
histogenesis of the lesion can be worked out with unusual completeness,
including its origin in the epithelial strands or rests in the cutis, the solid
and cystic masses among the coil-ducts, and the sacculated, adenoma-
tous, papilliferous glands embedded in the substance of the plasmoma.
In effect, this case, like Werther's, combines the less definite and more
fragmentary findings of a number of cases, and appears to substantiate
the most widely accepted view of the origin of this type of nevus.   Since
the lesion was apparently not congenital, it must be conceded that the
adenomatous degeneration occurred in later life as an incident in the
life-history of the nevus.   The mere fact that adenoma developed in
later life, in a region presumably predisposed, through the presence of
epithelial cell inclusions, to degenerative and neoplastic changes of this
type, need not, from the broader histogenetic standpoint, preclude the
use of the term "nævus syringadenomatosus."   The presence of the
cell-rests already referred to, the duct-like cords and cystic degenerations
in solid cellular inclusions, together with other evidences of epithelial
origin, the associated linear hypertrichosis, and the presence of appar-
ently normal ducts among the nevus types in the affected region, seem
to me to fully justify its designation as a nevus.   Werther reached the
same conclusion in his case on the basis of similar findings.

Epithelial metaplasia, as already remarked, is one of the most extra-
ordinary features of the sections, ranging from the basal-cell type, found
in the solid epithelial strands, through cuboid forms to the most remark-
able columnar transformation among the papillomatous ducts.   A care-
ful study of the hairy portion of the tissue removed was made with a
view to ascertaining whether any evidence of association of the neoplasm

with the pilosebaceous system could be made out, but without result. Normal sweat-glands, hair-follicles, and sebaceous glands were recognized, but no definite epithelial inclusions. Rothe cites Brauns as having recognized such an association in one case which apparently morphologically was none the less of the sudoriparous type. It is noteworthy that in the portion of the cutis in which the lesions arose in my case, as in Rothe's, hair and sebaceous glands seemed to be absent.

The question as to whether a malignant degeneration had occurred is of clinical interest. One general pathologist to whom the sections were shown believed the lesions to be sarcomatous, a judgment which has not infrequently been passed on pyogenic granulomas and which was not concurred in by dermatologists to whom the sections were submitted. With practical certainty, the glandular structure was that of an adenoma, and not of an adenocarcinoma, and no suspicious newly formed tubules or cords of cells were found out of association with the sweat-glands proper or in other parts of the cutis. Even where the proliferative process was most active, no signs of a tendency on the part of the glandular epithelium to leave the basement membrane could be discovered. Werther's case, resembling mine, was not regarded as malignant. Hedinger, however, believed his case to have become carcinomatous, and Rothe could not fully satisfy himself on the point. Another consideration justifying doubt in these cases is the occasional well-known difficulty in distinguishing between benign and malignant pictures when basal cells are involved. For this reason radical excision seemed justified in the present case.

The numbers of plasma cells present in certain portions of the granuloma seem to exceed the proportion of this type of cell found in the majority of pyogenic granulomatous lesions (Wile); Rothe also noticed the unusual numbers of plasma cells in the lesion which he observed on the scalp. He suggested that something in the composition of the granular detritus or the secretions from the hypertrophied tubules acted as a chemotactic agent. The present case afforded no opportunity to study this speculative explanation more closely or to offer other reasons for the presence of such numbers of these cells in the stroma of the neoplasm.

CONCLUSIONS

The case here presented offers the extremely rare combination of a nevus of the sudoriparous glands, with a highly vascular granuloma

containing large numbers of lymphocytes, plasma and mast cells, in a fibroblastic stroma, suggesting in many ways a granuloma pyogenicum or a vegetating dermatitis.

All stages in the histogenesis of such a nevus, according to the conception of origin in epithelial rests and inclusions (Cohnheim), seemed to be represented in the material from this case. While no frank evidence of the malignant nature of the neoplasm was found, the difficulty of distinguishing with certainty between the anlagen of these lesions in the cutis and malignant changes in an adenoma of this type, should be borne in mind in dealing with it clinically, and radical excision or large doses of roentgen rays given preference over less efficient methods of treatment.

REFERENCES

1. Blaschko, A.: Das Hidrocystoma papilliferum. Unna Festschrift, 1910, Vol. 2.
2. Brauns, T.: Ein Fall von ausgebreitetem Schweissdrüsen-Adenom mit Cystenbildung. Arch. f. Dermat. u. Syph., 1903, lxiv, 347–359.
3. Elliot, G. T.: Adeno-cystoma intracanaliculare occurring in a nævus unius lateris. Jour. Cutan. Dis., 1893, xi, 168–173.
4. Hedinger, E.: Zur Frage des Plasmocystoms (Granulationsplasmocytom in Kombination mit einem krebsig umgewandelten Schweissdrüsen-Adenom des behaarten Kopfes). Frankfurt Ztschr. f. Path., 1911, vii, 343–350.
5. Ormsby, O. S.: Syringoma. Jour. Cutan. Dis., 1910, xxviii, 433–444.
6. Paul, S. N., and Adamson, H. G.: A case of syringoma. Brit. Jour. Dermat., 1916, xxviii, 106–109.
7. Petersen, W.: Ein Fall von multiplen Knäueldrüsengeschwulsten unter dem Bilde eines Nävus verrucosus unius lateris. Arch. f. Dermat. u. Syph., 1892, xxiv, 919–930. Cited by Rothe, loc. cit.
8. Petersen, W.: Beiträge zur Kenntniss der Schweissdrüsen-Erkrankungen. Arch. f. Dermat. u. Syph., 1893, xxv, 441–479. Cited by Rothe, loc. cit.
9. Rothe, L.: Ueber einen Fall von Nævus syringocystadenomatosus (Hidrocystoma papilliferum) mit Plasmom. Arch. f. Dermat. u. Syph., 1912, cxiii, Orig., 887–906.
10. Sutton, R. L., and Dennie, C. C.: Possible interrelationship of acanthoma adenoides cysticum (multiple benign cystic epithelioma) and syringocystadenoma (lymphangioma tuberosum multiplex). Jour. Am. Med. Assn., 1912, lviii, 333–336.
11. Sutton, R. L.: Diseases of the skin. St. Louis, Mosby, 1916, p. 515.
12. Werther: Syringadenoma papilliferum (Nævus syringadenomatosus papilliferus). Arch. f. Dermat. u. Syph., 1913, cxvi, Orig., 865–870.
13. White, C. J.: Syringocystoma. Jour. Cutan. Dis., 1907, xxv, 49–60.
14. Wile, U. J.: Granuloma pyogenicum. Jour. Cutan. Dis., 1910, xxviii, 663–674.

EPITHELIOMA*

A. C. BRODERS AND W. C. MacCARTY

The term epithelioma, as the name implies, is a tumor composed of epithelium without any distinction relative to clinical malignancy or benignancy. If such specific cells as those lining the alimentary tract and comprising the sweat, sebaceous, buccal, salivary, and mammary glands, are still to be termed epithelium by histologists, then all so-called carcinomas are also epitheliomas. The term as utilized in this paper refers only to tumors of the epithelium of the skin, the glandular structures which are a part of it, and other structurally similar tissues, although the subject matter does not include such benign epitheliomas as warts, moles, corns, leukoplakias, epithelial horns, etc.

From November 1, 1904, to January 1, 1916, more than 2000 malignant epitheliomas were removed at the Mayo Clinic. The regional distribution comprises practically every portion of the human body which is covered by protective epithelium.

APPARENT TYPES

Structurally, the following apparent types are found, although they are probably not types, but the results of variation in origin and cellular differentiation: (1) Squamous cell epithelioma; (2) melanoepithelioma; (3) non-melanotic melanoepithelioma; (4) basal-cell epithelioma; (5) adamantine epithelioma, or adamantinoma; and (6) mixed epithelioma.

Squamous-cell epithelioma.—The squamous-cell epithelioma derives its name from the fact that the majority of its cells are of the squamous variety. Protoplasmic processes (spines or prickles) are often seen connecting the cells, hence the name spinal or prickle-cell epithelioma. This type has a wide anatomic distribution, being found in any portion of the surface of the body, and in such orifices as the mouth, nose, anus, and vagina. It is also found in the urinary tract, and it occasionally

occurs in the gallbladder and other places that normally contain columnar epithelium (Figs. 196, 215, 216).

Grossly, the squamous-cell epitheliomas present marked variations. They may be elevated, depressed, flat, papillary, cauliflower-like, ulcerated, smooth, soft, indurated, whitish, grayish, yellowish, or reddish. They usually start in leukoplakias, cracks, ulcers, or papillomas. The papillary form is frequently found in the urinary bladder (Figs. 187–200).

There is also an equal variation from a microscopic standpoint. They are made up of cells of various shapes, sizes, and degrees of differentiation (Figs. 212–223). Some show a marked tendency to cornify, especially those of the lip, inside of the cheek, floor of the mouth, the tongue, skin, penis, and vagina (Figs. 212, 217, 218), while others in the cervix, urinary bladder, tonsil, inside of the nose, nasopharynx, and the antrum of Highmore show little tendency to do so (Figs. 221 and 223). Those that originate on the inside of the nose and the nasopharynx are not infrequently diagnosed as some form of sarcoma; in fact, it often happens that a metastasis is discovered in one of the lymphatic glands of the neck before the original growth is located.

Germinal or regenerative cells are always present, in fact, one not infrequently sees cellular arrangement and morphology resembling all the layers of the epidermis. While some squamous-cell epitheliomas are composed of very large flat cells (Fig. 214), others are composed of very small ones, resembling those of spindle- and round-cell sarcomas (Figs. 220, 221, 223). Under the low power of the microscope they occasionally resemble the cells of a basal-cell epithelioma (Figs. 224, 225); these, however, under the high power, present definite prickles. Some epitheliomas show the morphologic characteristics of a spinal-cell and a basal-cell epithelioma. In fact, the two types of epithelium have been seen intimately connected in the same microscopic field (Fig. 226).

Melanoepithelioma.—Melanoepithelioma, as its name indicates, is an epithelioma containing melanin. It is possible for this tumor to grow in any part of the body where protective epithelium is found. It may be elevated, pedunculated, flat, or apparently subdermal, black, brown, or partially black and white, or brown and white. The pigment is not always evenly distributed throughout the tumor. In some instances the original tumors have very little or no apparent pigment and the secondary growth or growths will be jet black (Figs. 202, 203); the original tumor may be filled with pigment and the secondary growth or growths
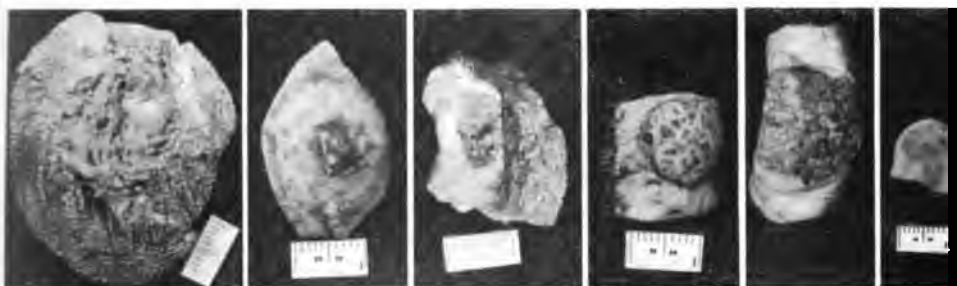
Fig. 187   Fig. 188   Fig. 189   Fig. 190   Fig. 191   Fig. 192

Fig. 187. —(A71140.)   Squamous cell epithelioma of scalp.
Fig. 188. —(A96946.)   Squamous cell epithelioma of temple.
Figs. 189, 190, 191, and 192. —(Cases A87015, A99484, A41521, and A92370.)   Squamous cell epithelioma of lip.
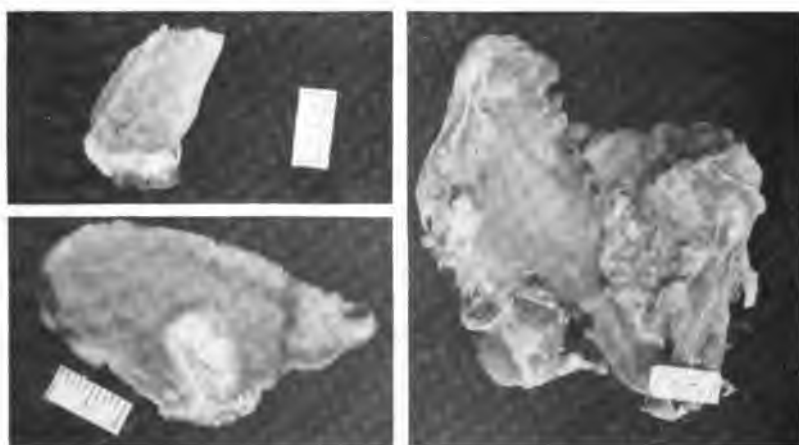
Figs. 193 and 194   Fig. 195

Fig. 193.- (A74417.)   Squamous cell epithelioma of lip.
Fig. 194. (A75909.)   Squamous cell epithelioma of tongue.
Fig. 195   (A89236.)   Squamous cell epithelioma of larynx.
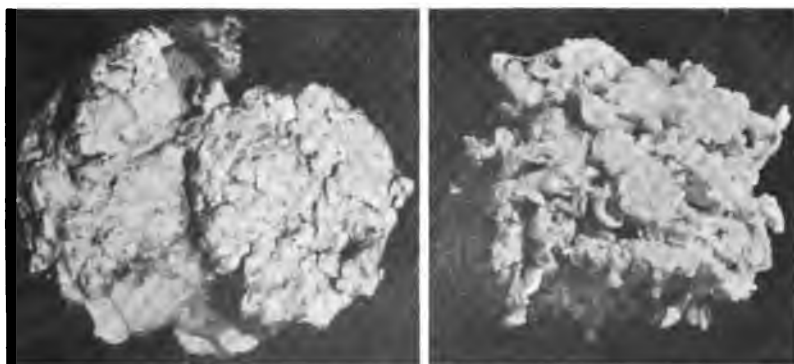
Fig. 196   Fig 197

Fig. 196 (at left). - (A163101.)   Squamous cell epithelioma of gallbladder.
Fig. 197. -(A191496.)   Papillary epithelioma of urinary bladder.
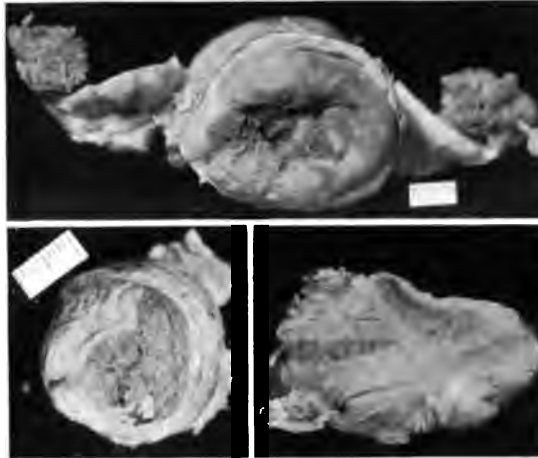
Figs. 198, 199, and 200

Fig. 198 (above).—(A62270.) Squamous cell epithelioma of cervix.
Fig. 199 (below at left).—(A38258.) Squamous cell epithelioma of penis.
Fig. 200.—(A38258.) Section of epithelioma shown in Fig. 199.

Fig. 201   Fig. 202

Fig. 201.—(A57193.) Melano-epithelioma of right leg.
Fig. 202.—(A143701.) Melano-epithelioma over left scapula.

Fig. 203.—Metastatic melano-epithelioma of left axillary glands, secondary to growth shown in Fig. 202.

Fig. 211.—(A59772.) Adamantinoma, showing solid areas and cysts.

Fig. 204.   Fig. 205.   Fig. 206.   Fig. 207   Fig. 208   Fig. 209   Fig. 210

Fig. 204.—(A186088.)   Section of a non-melanotic melano-epithelioma over left shoulder with metastases into glands of left axilla.
Fig. 205.—(A50531.)   Basal-cell epithelioma of scalp.
Fig. 206.—(A55848.)   Basal-cell epithelioma of nose.
Figs. 207 and 208.—(A33173, A96196.)   Basal-cell epithelioma of eyelid.
Fig. 209.—(A96226.)   Basal-cell epithelioma of forehead.
Fig. 210.—(A59758.)   Basal-cell epithelioma of cheek.

Figs. 212 to 220

Fig. 212.—(A64692.) Squamous cell epithelioma of lip showing cornified areas.
Fig. 213.—(A38258.) Squamous cell epithelioma of penis, same as Fig. 199.
Fig. 214.—(A89236.) Squamous cell epithelioma of larynx. Note the large cells. Same as Fig. 195
Fig. 215. Squamous cell epithelioma of gallbladder. (A163101.) Same as Fig. 196 (low power).
Fig. 216.—(A163101.) High power of Fig. 215, showing intercellular bridges or prickles.
Fig. 217. (A38455.) Squamous cell epithelioma of cheek showing partial cornification of cells.
Fig. 218.—(A22297.) Squamous cell epithelioma of gland of neck, secondary to epithelioma of the floor of the mouth. Note the cornification of practically all of the cells.
Fig. 219.—(A53221.) Squamous cell epithelioma of cervix, showing invasion of the mucous glands by the epithelioma cells.
Fig. 220.—(A55450.) Squamous cell epithelioma of gland of neck, secondary to epithelioma of larynx. This kind of epithelioma is not infrequently diagnosed an endothelioma.
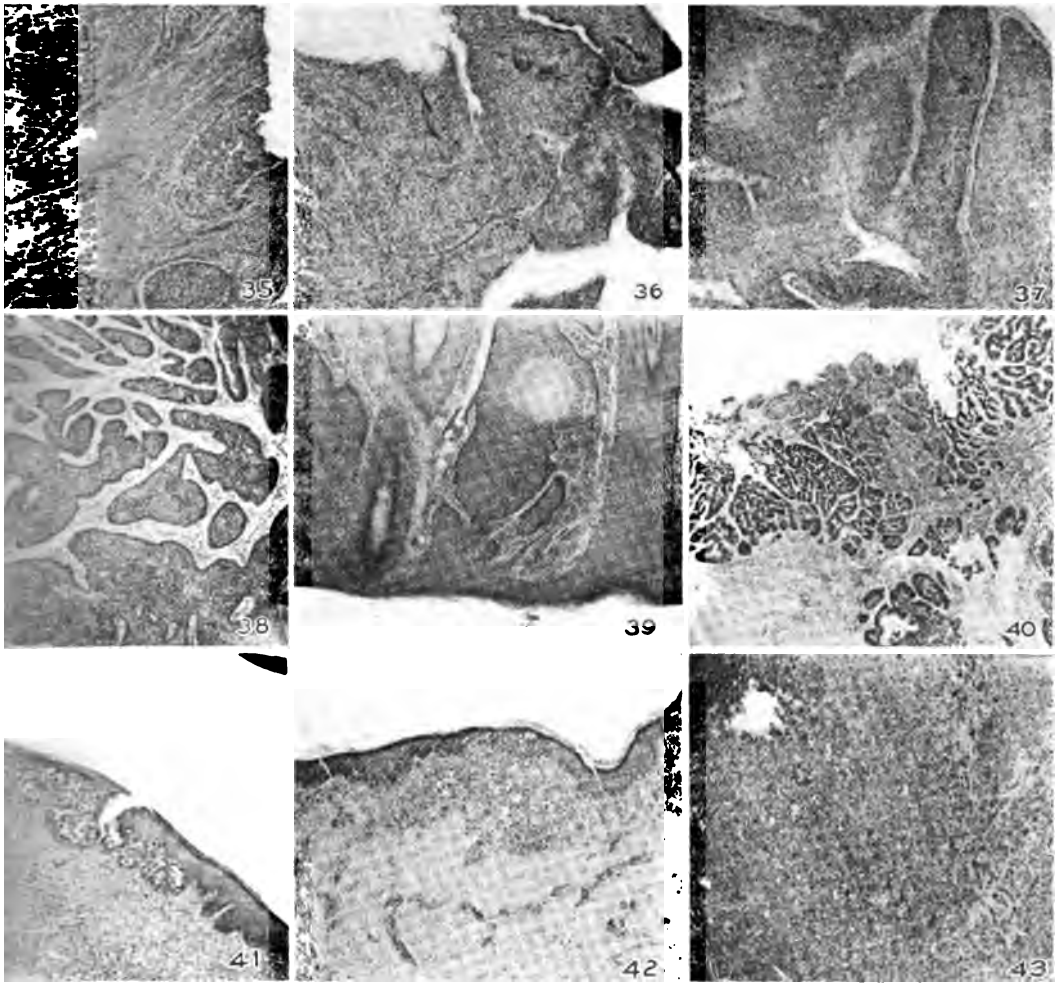
Figs. 221 to 229

Fig. 221.— (A62270.) Squamous cell epithelioma of cervix, showing invasion of muscle by epithelioma cells, same as Fig. 198.
Fig. 222.- (A191496.)   Papillary epithelioma of urinary bladder, same as Fig. 197.
Fig. 223.—(A94680.)   Squamous cell epithelioma of tonsil. Metastases from this kind of epithelioma are not infrequently diag-
nosed some kind of sarcoma.
Fig. 224.—(A114881.)   Squamous cell epithelioma of the cheek with a low power appearance of a basal-cell epithelioma.
Fig. 225.—(A42356.)   Squamous cell epithelioma of the eyelid with a low power appearance of a basal-cell epithelioma, excepting
be epithelial pearl.
Fig. 226.—(A20310.)   Epithelioma on the outside of nose, showing squamous and basal cells intimately connected in the same
field. The basal cells present a gland formation.
Fig. 227.— (A99046.)   Early melano-epithelioma of the labium.
Fig. 228.—(A57193.)   Melano-epithelioma of the right leg, same as Fig. 201.
Fig. 229.—Metastatic melano-epithelioma of a gland of the right groin, secondary to a melano-epithelioma of the leg, same as
Fig. 228.
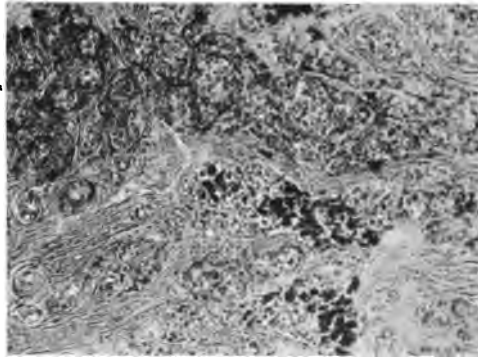
Fig. 230

Fig. 230. (A80193.) Melano-epithelioma of the skin of the
groin. Note the alveolar arrangement.

Fig. 231
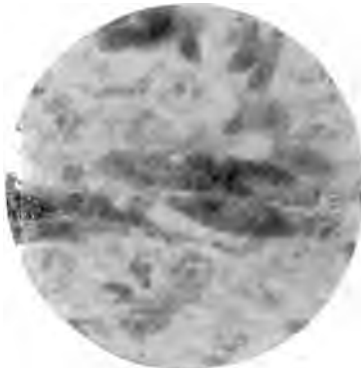
Fig. 232
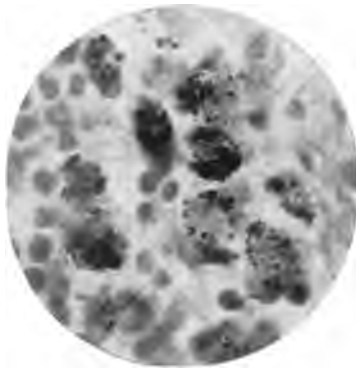
Fig. 233

Figs. 231, 232, and 233. (A105603 and A36641.) Photomicrographs showing variety of cells
which are found in melano-epitheliomas.
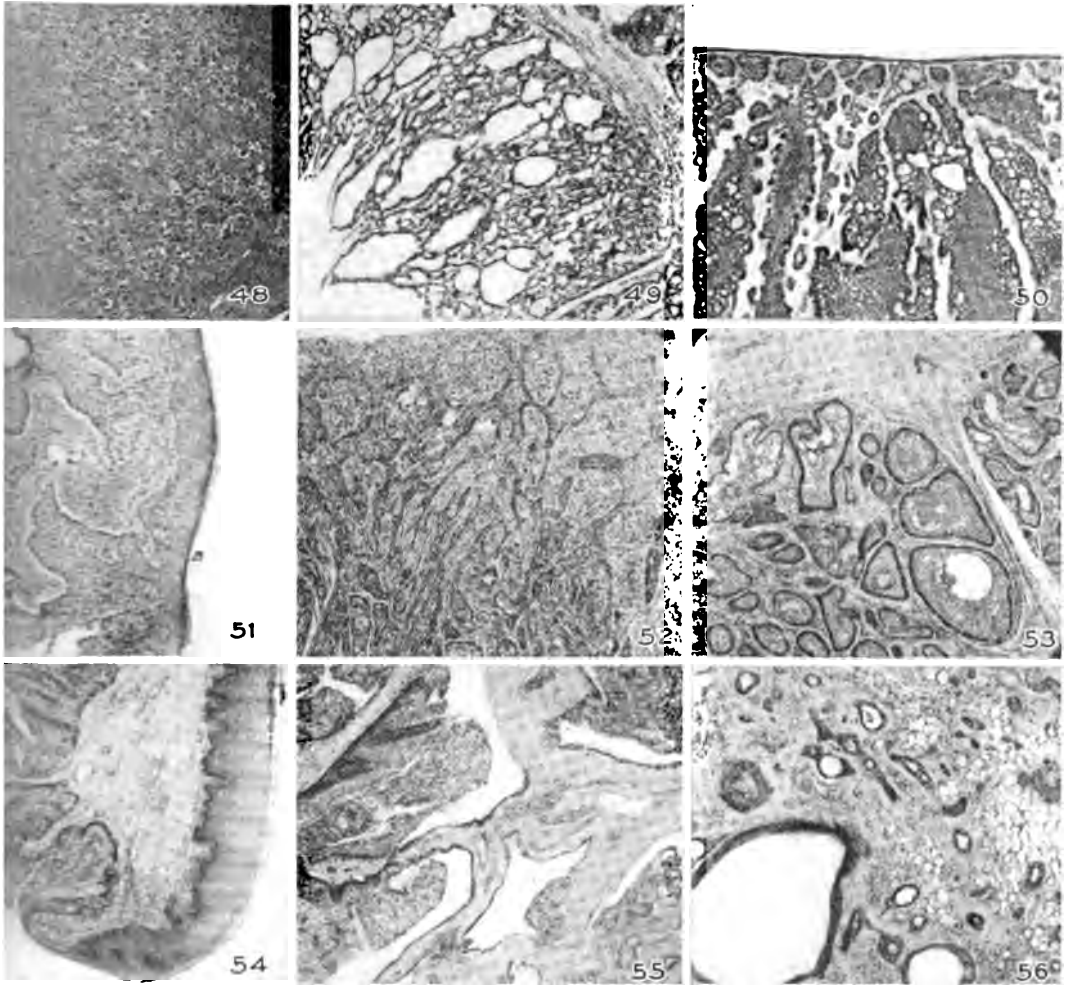
Figs. 234 to 242

Fig. 234.– (A186088.)   Non-melanotic melano-epithelioma, same as Fig. 204.
Fig. 235.– (A38151.)   Basal-cell epithelioma of the outside of nose.   Note the close resemblance to thyroid.
Fig. 236.–(A33009.)   Basal-cell epithelioma of forehead, showing gland-like and solid areas.
Fig. 237 – (A38366.)   Basal-cell epithelioma of nose, showing solid plugs of cells.
Fig. 238.   (A68435.)   Adamantinoma, showing direct connection with the epithelium of the gum.
Fig. 239.– Section from center of tumor shown in Fig. 238, showing different types of cells and early cyst formation.
Fig. 240.– (A147265.)   Mixed epithelioma of palate showing direct connection of tumor cells and epithelium.
Fig. 241.—Different field in same case as Fig. 240, showing squamous and gland epithelium intimately connected.   Note the mucous glands in one corner.
Fig. 242. -(A156093.)   Mixed epithelioma of palate, showing squamous epithelium and glands similar to those of the breast in the same field.
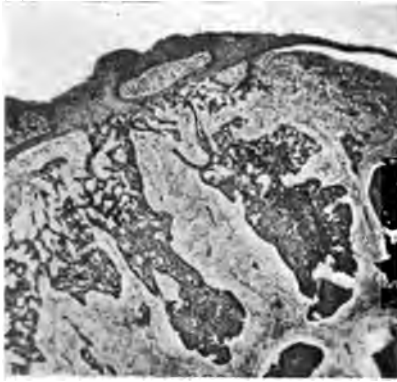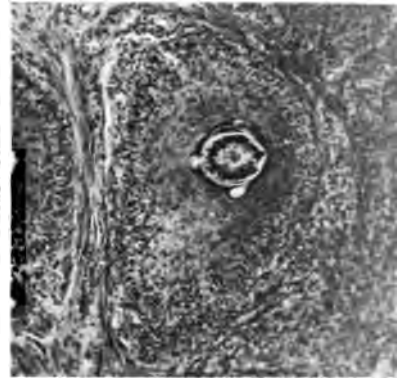
Fig. 243   Fig. 244   Fig. 245

Fig. 243.—(A71761.)   Basal-cell epithelioma of cheek.   Similar to Fig. 236.
Fig. 244.—Early basal-cell epithelioma of forehead. (A98228) same as Fig. 209.
Fig. 245.—(A96196.)   Early epithelioma of a hair follicle.

be free or practically free from it. Microscopically, spheroid, spindle, and ovoid cells, with or without pigment, may be seen (Figs. 231, 232, and 233). It has a marked tendency toward alveolar formation (Figs. 228 and 230). This type of epithelioma has been discussed in a previous article by Broders and MacCarty.[2]

Non-pigmented melanoepithelioma.—This type of epithelioma has all the morphologic and clinical characteristics of the melanoepithelioma except pigment. It is usually diagnosed as some form of sarcoma (Figs. 204 and 234).

Basal-cell epithelioma.—The tumor is commonly known as the rodent ulcer. Like other epitheliomas, it may be found on any surface of the body covered with protective epithelium. However, it is most often found on the cheek, outside of the nose, temple, eyelid, and forehead. It often appears in the skin as an elevated whitish nodule resembling an adenoma or cyst of a sebaceous gland, as an ulcer with indurated borders, or as a scaly lesion which exfoliates its superficial layers, leaving a shiny surface, but showing little tendency to heal completely (Figs. 205–210). The latter form is usually found in persons who are exposed to intense sunlight. It is a frequent occurrence in the sunburnt skin of farmers.

Microscopically, the tumor presents an equal variation of the squamous-cell type. Its cells may be long and slender, short and thick, or round, oval, or spindle-shaped. In addition to the variation of cellular morphology there is great variation in the arrangement of its cells. Some are alveolar or gland-like, the latter condition resembling the arrangement of the thyroid; others have a cactus-like appearance; some are composed of diffuse or circumscribed solid masses of cells, and others have a combination of different forms (Figs. 235–239). It derives the name basal-cell from the fact that its cells tend to differentiate to a form similar to the cells of the basal or germinative layer of the epidermis. As a matter of fact, all tumors arising in protective epithelium are basal-cell epitheliomas—the only feature distinguishing them is their cellular differentiation. Undoubtedly basal-cell epitheliomas are not infrequently diagnosed endotheliomas, alveolar sarcomas, round-cell sarcomas, spindle-cell sarcomas, and adenocarcinomas. The cells of a pure basal-cell epithelioma are not supposed to contain prickles or spines, but on account of their occasional presence it is often difficult to determine whether an epithelioma should be called a basal- or squamous-cell epithelioma. Prickle-cells are often found in so-called basal-cell

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epitheliomas and basal-cells can always be seen in squamous-cell epitheliomas.

Adamantine epithelioma or adamantinoma.—This type of neoplasm has been taken into consideration because of its marked cellular resemblance and close relationship to the squamous-cell epithelioma. There are differences of opinion as to its histogenesis. Falkson[4] held that in the formation of enamel-organs for the several teeth there was a surplus and that these additional dental germs were the origin of the adamantinomas. Malassez[7] advanced the theory that they arise from epithelial rests or paradental epithelial débris. Scudder[10] states: "There is very great likelihood that the cells of the primary epithelial cord, having served their usefulness, are detached from the original enamel-organ cells and may be the cells, which persisting, form the tumor under consideration." Buchtemann[3] and Kolaczek[5] believe that these tumors originate from the mucous membrane or the mucous glands of the mouth. Bland-Sutton[1] says: "They probably arise from persistent portions of the epithelium of enamel-organs."

The number of theories which have been advanced relative to this tumor naturally leads one to believe that very little is known of its origin. It is usually located in the lower jaw at or near the angle, although a certain proportion are located in the upper jaw. Some of them attain the size of a grape-fruit. On gross section the tumor proper is seen to be incased in a thin, bony capsule, made up of cystic and solid areas (Fig. 211). The cysts range in size from 1 mm. to 3 cm. in diameter and are filled with a yellowish-brown, mucoid fluid. They are separated by bony or fibrous septa. The cut surface of a fresh specimen presents reddish, granular solid areas between which are multiple small cysts.

Microscopically, the tumor has a connective-tissue stroma and columns of variously shaped masses of epithelial cells. In one instance the epithelial columns showed direct connection with the epithelium of the gum (Fig. 240). This fact tends to suggest that this neoplasm arises from the regenerative or basal-cells of the epithelium of the mucous membrane, which would be in accord with the histogenesis of all other types of epitheliomas. Deeper down in this same tumor cellular masses with the early cyst formation may be seen (Fig. 241).

The adamantinoma presents two distinct types of epithelial cells (Fig. 241). The outer or columnar cells, which are undoubtedly the germinal or regenerative cells, correspond to the columnar germinal or regenerative cells of the enamel-organ. These also correspond to the basal or germinal cells of the epidermis from which the enamel-organ is

derived. The polygonal and stellate cells, which are so characteristic, represent an advanced stage of differentiation. They sometimes contain prickles which also have corresponding cells in the enamel-organ and resemble the prickle-cells of the epidermis. These cells appear to disintegrate and form cysts before they reach the stage of cornification. Similar cysts are found in squamous-cell epitheliomas as a result of cell disintegration. New[8] has written an article describing this type of epithelioma.

Mixed epithelioma.—This type of epithelioma is met with infrequently. It is usually located in the palate, although it may occur in other locations. Two cases were observed in the Mayo Clinic in which the tumor was in the palate. The first occurred in a girl sixteen years of age. It was fairly regular in outline and measured 2 by 2 by ½ inches. When a specimen was removed for microscopic diagnosis an ounce of straw-colored fluid escaped from what appeared to be a cyst. Microscopically, the tumor contained squamous epithelium directly connected with the mucous membrane of the palate (Fig. 242). Other areas showed masses of squamous epithelium separated by fibrous septa, plus the presence of mucous glands and gland-like structures that were continuous with the squamous epithelium (Fig. 243).

The second tumor occurred in a man sixty-four years of age. It was encapsulated, measured 1 by ½ by 1 inch, and on section was found to be a solid mass free from mucus. Microscopically, the tumor contained numerous gland-like masses, made up of squamous epithelium in which the central cells had degenerated in a similar manner to that in an adamantinoma. This tumor differed from the first in that it did not contain mucous glands. It also contained what appeared to be true glands, like those found in the breast with the exception of mammary grouping (Fig. 244). Similar tumors have been found in other locations.[9]

DISCUSSION

In view of the fact that epitheliomas vary so much in the structure of the cells and their arrangement it seems wise to consider the anatomic possibilities of origin and other reasons for the apparent types.

A clear conception of the structural nature and biologic significance of such an interesting and important group of neoplasms cannot be obtained without a knowledge of the embryologic development of the skin and its accessory organs.

If the life-history of the skin is traced, it is begun with the ectoderm of the three-layer stage of embryologic development. This layer of

partially differentiated epithelium becomes more highly developed to form the so-called skin of the embryo. At first it is composed of one layer of cuboid cells, which, with the further development of the embryo, becomes differentiated to form two or more layers of cells—the outer layer differing from the first layer in being flatter or less cuboid, with their long axes parallel with the surface of the body.

With both antenatal and postnatal development the secondary layers become more differentiated and less like their immediate predecessors, which in this stage embryologists have termed the "stratum germinativum" of the skin or the germinating layer of the epidermis.

The history of the cells of this layer proves that they retain the power of divergence into several structural and functional derivatives. It may be spoken of as a plastic layer, at least in the embryo. This expression of its broad functional capacity is based on its behavior in the development of the appendages of the skin, namely, hair, nails, teeth, sweat-glands, sebaceous glands, buccal glands, and mammary glands.

Histologic specimens taken through the embryonic skin and subcutaneous tissue in various portions show developmental activities of the stratum germinativum other than the production of epidermal cells.

The diversity of possible variation of products of this layer of cells is not only visible in embryologic development, but it may be seen in the change from columnar epithelium of the lower rectum, the uterine cervix, the urinary bladder, and the mouth, in all of which organs the regenerative cells produce squamous or stratified epithelium instead of columnar epithelium when a protective occasion arises.

It has been shown definitely that a chronic destruction of specific tissues gives rise to certain definite histologic, biologic, and clinical phenomena in the regenerative cells of such tissues.

These are characterized histologically by hypertrophy, hyperplasia, and migration, biologically by hyperactivity, reproduction (neoplasia), and migration, and clinically by benignancy, uncertainty, and malignancy.[6] It has been shown, further, that the cells of the migratory (malignant) stage, when they acquire an environment somewhat similar to their normal environment, attempt to differentiate into the tissue cells for which they were originally intended. This is seen in the case of glandular tissues as well as protective epithelial tissues. In the cases of the epitheliomas under discussion in this paper there are several possible points of origin. The germinative cells of the epidermis, sebaceous glands, sweat-glands, oral and nasal mucous glands, and the hair-follicles all constitute possible sites of origin for neoplasia. Neo-

plasia arising in the first, second, and fifth of these structures has already been seen by the writers.

Theoretically one should be able to determine the origin of neoplasia from the character of the differentiation in the new-growth. While this may be theoretically possible, it is only infrequently possible because malignant neoplastic cells rarely if ever become completely differentiated; if they did, they would produce benign conditions. Cells in the partially differentiated portions of malignant neoplasms which are more nearly morphologically like certain tissues than like any other tissues are seen. This is especially true, as has been stated in the cases of certain epitheliomas in which the cells undoubtedly resemble cornified epithelium and sebaceous cells. In the cases of hair-follicles, the only evidence that exists from the possible origin of some of the epitheliomas in these structures is the fact that early migratory neoplastic cells have been demonstrated arising in the stratum germinativum of the follicles (Fig. 245).

There is one other possibility within the range of analogy to facts as they occur in the human body. From the reaction of regenerative cells of tissues which, by the so-called process of metaplasia, become transformed from columnar cells into stratified squamous cells, it seems possible for the regenerative cells of any of the accessory organs of the skin to produce cells similar in structure to those of any other accessory organ. This possibility is merely mentioned to stimulate investigation, and in no way is it held to be responsible for any of the conditions reported herein.

In presenting this brief description of typical malignant conditions arising in the skin, its accessory organs, and analogous epithelial structures practically no attempt has been made to report the clinical aspects of the subject. The results of detailed gross, histologic, and cellular studies with their clinical significance will be presented elsewhere in the near future.

REFERENCES

1. Bland-Sutton, J.: Tumors, innocent and malignant, their clinical features and appropriate treatment. London, Cassell, 1901, p. 48.
2. Broders, A. C., and MacCarty, W. C.: Melanoepithelioma. A report of 70 cases. Surg., Gynec. and Obst., 1916, xxii, 28–32.
3. Buchtemann: Cited by Borst, M.: Lehre von den Geschwulsten, 1902, ii, 607.
4. Falkson, R.: Beitrag zur Entwicklungsgeschichte der Zahn-Anlage und Kiefer-Cysten, Königsberg, 1879, 33 pp.
5. Kolaczek: Cited by Borst, M.: loc. cit.
6. MacCarty, W. C.: The histogenesis of cancer of the breast and its clinical significance. Surg., Gynec. and Obst., 1913, xvi, 441–459.
7. Malassez: Arch. de physiol. norm. et path., 1885, v, 129.
8. New, G. B.: Cystic odontomas. Jour. Am. Med. Assn., 1915, xiv, 34–39.
9. New, G. B.: Adenoma of the palate. Ann. Otol., Rhinol., and Laryngol., 1916, xxv, 687–700.
10. Scudder, C. L.: Tumors of the jaws. Phila., Saunders, 1912, p. 174.

A LUETIN REACTION IN SYPHILIS PRODUCED BY AGAR

WITH A BRIEF CONSIDERATION OF ITS MECHANISM *

J. H. STOKES

The enthusiasm with which cutaneous tests for diagnostic purposes have been incorporated into clinical practice is a striking tribute to the uncritical frame of mind in which we are prone to receive what promises to present the golden combination of simplicity and usefulness. Few better illustrations of this ready acceptance of the plausible as gospel could be found than the reception accorded the luetin reaction.

Before Sherrick[1] noted the effect of iodids on the reaction, the literature was flooded with favorable, but now almost worthless, reports, from a large percentage of which it is impossible to determine what controls were used and in which controls were even admittedly dispensed with. Here and there more critical observers called attention to the uncertainties of the reaction, and to the behavior of some of the control suspensions distributed with authentic Noguchi preparations of luetin. My own interest in the specificity of the reaction and its possible mechanism was first aroused by the production of a very convincing luetin reaction in a case of late syphilis in which I was studying the sensitization phenomena of psoriasis by means of intradermal injection of an emulsion made from normal skin. Following this I discovered to my surprise that as the apparent result of a series of injections of homologous protein emulsions made from our own skins, my skin, and that of my assistant reacted to a typical colloid (agar) in a way clinically identical with the tardive luetin reaction.[2] This sensitivity apparently diminished slowly after the experiments were discontinued. Having in the meanwhile developed a theory of the mechanism of such reactions based on the newer physicochemical conceptions of anaphylactic phenomena, founded on the work of Bordet, Mutermilch and Kopaczewski, Keyser and Wassermann, Jobling and Petersen, Novy and DeKruif, and others,

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I undertook to see whether a typical colloid suspension, whose properties as an anaphylatoxin-former were well understood, would give rise to reactions like the luetin reaction, in states of dermal hypersensitivity such as we know to exist in a certain percentage of syphilitics. The purpose of this paper is to report the success of the attempt based on these theoretic considerations, the fuller consideration of the significance of the result being deferred for a future paper. Sherrick[1] and Kolmer[2] have both noted that a reaction occurred under potassium iodid, but neither has observed its reaction when potassium iodid has not been administered, possibly because of its slow development, which sometimes calls for a period of observation of not less than fourteen days fully to identify a positive reaction.

Agar presents the striking advantage over many of the bacterial
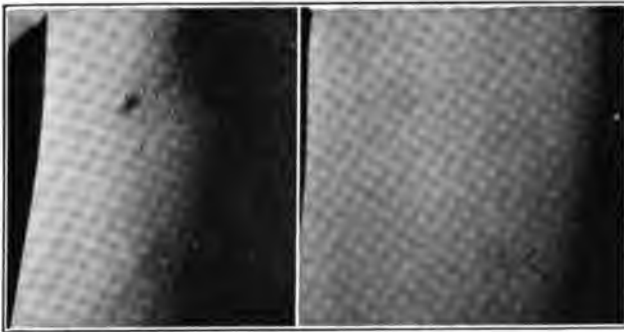
Fig. 246.—The positive (left) and negative (right) reactions to agar on the fourth day after injection of 0.1 c.c. of a 0.7 per cent. suspension. Both patients (women) had syphilitic periostitis and total inhibition. Wassermann tests. The oil controls are negative.

protein suspensions, toxins, etc., used for intradermal tests, that its behavior in vitro and in vivo has been fairly well worked out in the development of newer immunologic conceptions. It has been shown with reasonable definiteness that as a colloidal suspension it is able, by an absorptive action, to render homologous serums, which are supposedly non-toxic, extremely toxic, and that this effect is related to the colloidal properties of blood-serum. This generation of anaphylatoxin by agar, its ability to disturb colloidal equilibrium along certain constant lines without itself being broken up or subjected to chemical change, makes it a very favorable medium for the study of the colloidal equilibrium of tissues in normal and disease conditions. The ability to show that agar in proper concentration, intradermally injected, gives

rise, in states of dermal hypersusceptibility, to inflammatory reactions clinically similar to the luetin reaction, suggests that the mechanism of luetin is at least in part physical and not chemical. Moreover, it is

Fig. 247.—The positive shown in Fig. 246 (left), on the eighth day. Hemorrhagic pustule.

possible that the hypersensitiveness which permits of such a reaction is also a physical state, the peculiarities and origin of which can be worked out along physical lines of investigation. As a result of my studies of the behavior of this substance when substituted for luetin, I am inclined to regard the hypersensitiveness of the skin in late syphilis, familiarized as *Umstimmung* by the studies of Neisser, Finger and Landsteiner, and others, as a colloidal phenomenon, and to regard the action of luetin largely as that of a mixture of colloids, the adsorbent action of which makes possible the liberation of anaphylatoxin in the tissue in which it is injected, with a resulting inflammatory reaction about the site of injection. Critical analysis of the composition of luetin

Fig. 248.—The reactions shown in Fig. 246 on the ninth day: right, positive; left, negative.

as originally prepared by Noguchi[4] justifies this belief, since the anaphylatoxin-forming properties of ground Spirochæta pallida have been demonstrated[5] as well as those of agar. To justify this theory it remained to show that, independent of the influence of iodids, a reasonable percentage of

syphilitics would react to a colloidal adsorbent in suitable concentration in a way clinically similar to the luetin reaction. While the series of cases here reported is not large, it certainly suggests that there is a hitherto only partly appreciated element of non-specificity in this reaction. It is not proposed to attack the clinical serviceability of luetin in the diagnosis of obscure syphilis, or to propose agar as a substitute without considerably more study. On the other hand, it cannot but give us pause in our enthusiasm for the diagnostic value of luetin and its immunologic significance to find that not only can the reaction be utterly invalidated by a little potassium iodid, but that it can be perfectly imitated by a sterile colloidal suspension which experimental studies seem to indicate remains chemically inert and acts presumably only through

Fig. 249.—A positive reaction on the third day, which then subsided. Rated as doubtful and discarded. Hereditary syphilis with a negative Wassermann test.
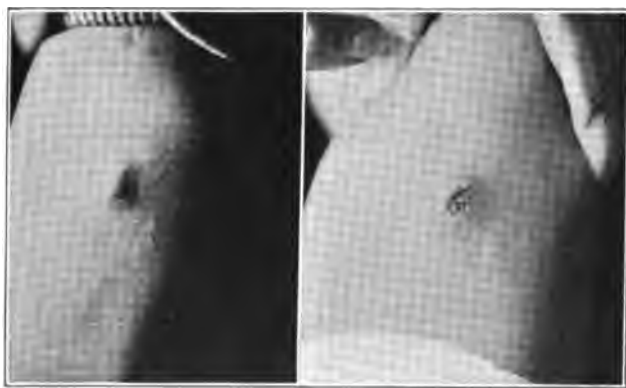
Fig. 250.—A reaction which was positive on the third day, subsided and lighted up again on the eighth; left, pustulobullous lesion on the eleventh day; right, ruptured and drying pustule on the fourteenth day. Tabes dorsalis, blood Wassermann test positive, no iodids. ·

its physical properties. The reaction to agar as here described was negative in a variety of non-syphilitic conditions and in the normal persons on whom it was tried. It was mildly positive on five

occasions in clinically and serologically non-syphilitic persons, two of whom, however, had gonorrheal arthritis, and three of whom had been receiving massive injections of vaccines, the ability of which to alter the colloidal state of the body and bring about so-called ferment mobilization has been suggested by the work of Jobling and Petersen[6] and others.

Fig. 251.—Drying pustule on the ninth day in latent syphilis with a positive Wassermann test. Mercuric succinimid intramuscularly and salvarsan; no iodids.

The preparation used in my work has been a sterile 0.5 per cent suspension of granular or powdered agar in physiologic sodium chlorid solution (unfiltered), sterilized in the autoclave. In more recent reactions I have used a 0.7 per cent suspension. Several preparations of agar have been employed to eliminate the possibility of the presence of peculiarities due to the method of manufacture. The gel, undiluted, is injected intradermally in amounts of 0.1 c.c. An equal amount of mechanical trauma, inflicted by the injection of 0.1 c.c. of sterile olive oil as a control, has failed thus far to produce any positives, even when the agar reaction is positive. The course of the reaction is quite similar to that of luetin, with emphasis on the tendency to tardive reaction. Pustulation occurs, in marked cases, usually after the fifth day, and often as late as the tenth or twelfth. The pustule is rather more hemorrhagic than the typical luetin lesion, and occasionally bullous. Cultures from the fluid in several lesions and mi-

Fig. 252.—Fifteenth-day pustule, early secondary syphilis, receiving only intramuscular injections of mercuric salicylate.

croscopic examinations have shown it to be sterile. There is a distinct variation in the intensity of the reaction with the concentration of the agar, and it is my impression also that certain obscure properties of the colloid suspension, such as may result from shaking it before it has gelled, and chilling it affect its behavior. Even though they seem to have been made up in the proper percentage strength, preparations occasionally give unsatisfactory results, especially when they are thin and watery or very flocculent. Variations of this type can scarcely have been avoided in the manufacture of luetin, and may

Fig. 253.—Tardive pustulobullous lesion, twenty-first day. Nodulo-ulcerative late syphilid of the face; gumma of the palate. Salvarsan; mercuric succinimid intramuscularly; no iodids.

explain the occasionally erratic behavior of even authentic preparations.

It must be apparent that luetin, as a marketable preparation for the diagnosis of syphilis, is an uncertain entity and that, to say the least, it needs standardization.

In the summary of results in Table 1, reactions have been interpreted as positive with conservatism. Slight infiltrations, bluish macules, and even small papules which failed to show the tendency to central softening have been rated as doubtful and discarded. No reaction has been considered until after the third day. Marked reactions are unmistakable, and give rise to a deep pustule which may enlarge as if by process of peripheral digestion of the tissues, until it becomes flaccid or is evacuated, discharging a grumous pus and leaving a marked bluish or purple scar.

Fig. 254.—Negative reaction in bullous erythema multiforme. Patient seen some weeks later: no signs of lighting up.

The reaction is slower to develop than the luetin, and on the whole more indolent, and it is this tardive tendency perhaps which has caused other

observers to overlook it. The inflammatory areola, which may disappear after the second day, may reappear when the reaction begins to light up. The reaction is usually markedly accelerated by iodids, forms a higher, firmer nodule, and evacuates sooner. In two cases, one of latent syphilis and one of actinomycosis (moribund), the reaction failed to develop even under liberal doses of potassium iodid.

In the Chicago cases, studied through the courtesy of Dr. F. G. Harris at the Cook County Hospital, the percentage of positives was higher than on my own service at Rochester, possibly because the former patients were subject to the uncertainties of outside treatment with possible iodid administration, whereas in the cases of the latter the question of iodid administration was effectually eliminated, the majority of the patients being under my care for some weeks without iodids before the reactions were started, and the diagnosis of syphilis having been made on most of them for the first time when they entered the Clinic. In the Chicago series a 0.5 per cent suspension was used, and in the Rochester series a 0.7 per cent suspension. Suspensions of 0.1 per cent and 1 per cent were tried, but gave unsatisfactory and usually negative results. In comparing with my results the percentage of positives obtained for

Fig. 255.—Iodid reaction to agar. Pustule ruptured on the sixth day. Patient with syphilitic aortitis receiving salvarsan, intramuscular injections, and 20 grains of potassium iodid, three times a day.

luetin by observers before the influence of iodids was recognized, it should not be forgotten that the published percentages for luetin are undoubtedly inflated by the unsuspected effect of iodids and should therefore be lower than the reports indicate.

The non-syphilitic cases in which negative reactions were obtained included 6 cases of psoriasis, 3 of eczema, 2 of toxic erythema, 1 of chancroid, 3 of pulmonary tuberculosis, 1 of acne vulgaris, 1 of pellagra, and 1 of actinomycosis of the appendix.

A positive reaction was obtained in one case in which syphilis certainly was not present—a case of urticaria pigmentosa in an adult. Of

three cases of gonorrheal arthritis, two were positive to agar with negative Wassermanns, but both of these patients had been receiving vaccines with marked reactions and, moreover, syphilis could not be excluded. In another case from which syphilis could not be excluded but which was Wassermann-negative, the patient reacted positively while receiving vaccine for a sycosis, with marked febrile responses. With reference to gonorrhea it will be recalled that Boas and Ditlevsen,[7] among others, secured positive luetin reactions in several patients with gonorrhea in their series, and even in persons who were apparently normal.

In the Chicago series of twelve patients with syphilis, two reactions were discarded as doubtful, and seven (70 per cent) reacted positively.

In the Rochester series (0.7 per cent agar used), of thirty-five patients with syphilis, five reactions were discarded as doubtful, and fifteen (50 per cent) reacted positively. Rating the doubtfuls as negative, the percentage of positives was 42.3 per cent.

Table 1 combines the two series, omitting all doubtful reactions.

It is interesting to note that positive reactions were obtained for all but two of nine tabetics (about 78 per cent). The increasing frequency of positives in the later stages of the disease is in keeping with the behavior of luetin.

From my observations as the work has progressed I have gained the impression that the positive reaction can be brought out by intensive treatment, exclusive of iodid administration, notably by intramuscular injections of mercurial salts. This is in keeping with the opinion of observers of syphilis and will be discussed with the theoretic considerations in another paper.

CONCLUSIONS

Agar hydrosol, from 0.5 to 0.7 per cent in physiologic sodium chlorid solution, when injected intradermally in doses of 0.1 c.c., gives reactions clinically similar to those produced by luetin. Controls of equal amounts of sterile olive oil, producing similar trauma, do not give rise to reactions.

The agar reaction differs from the luetin reaction chiefly in a tendency to a more torpid course and a slower development.

Papular and pustular reactions may be produced, the latter being somewhat more hemorrhagic than those produced by luetin.

The percentage of positives in known syphilitics, eliminating doubtful reactions, varied in two series, aggregating forty cases, from 50 to 70 per cent.

The normal persons and non-syphilitics in my series did not react.

The only positive case in which syphilis seemed to be eliminated was a case of urticaria pigmentosa with factitial urticarial phenomena. Two patients with gonorrhea in a total series of 76 reacted positively. Both were receiving vaccines with marked reactions. One patient with sycosis barbæ, receiving vaccines with marked reaction, also reacted positively to the agar.

The influence of iodids could be eliminated from the series in which 50 per cent reacted positively.

The positive reaction to agar, as brought about by the internal administration of iodids, was observed in typical form in three cases. It is simply a severe form of the luetin and agar reactions. In two cases in which iodids were being administered the reaction to agar was negative.

The cutaneous reaction to both luetin and agar in syphilis is interpreted as non-specific in character and as a colloidal adsorption phenomenon in a hypersensitive or labile skin. The theoretic considerations on which this view is based have been published in part, and a review of their possible bearing on the immunologic mechanism of syphilis will be published shortly.

TABLE 1.—RESULTS OF TESTS

FORM OF SYPHILIS	POSITIVE NUMBER	POSITIVE PER CENT	NEGATIVE NUMBER
Primary	2	66	1
Latent	2	40	3
Secondary	3	43	4
Tertiary	6	55	5
Cerebrospinal	8	62	5
Total early	..	46.6	..
Total late	..	58.3	..

The importance of a further study and standardization of preparations of luetin is suggested. The foregoing studies suggest that the fragmented Spirochætæ pallidæ are not indispensable in the production of the reaction clinically known as the luetin test.

REFERENCES

1. Sherrick, J. W.: The effect of potassium iodid on the luetin reaction, Jour. Am. Med. Assn., 1915, lxv, 404–405.
2. Stokes, J. H.: Studies on intradermal sensitization, II, An intradermal reaction to agar and an interpretation of intradermal reactions, Jour. Infect. Dis., 1916, xviii, 415–436.
3. Kolmer, J. A., Matsunami, T., and Broadwell, S.: The effect of potassium iodid on the luetin reaction, Jour. Am. Med. Assn., 1916, lxvii, 718–719.
4. Noguchi, H.: A cutaneous reaction in syphilis, Jour. Exper. Med., 1911, xiv, 557–568.
5. Nakano, H.: Ueber Kutireaktion bei Syphilis, Part I, Arch. f. Dermat. u. Syph., 1913, cxvi, 281–312.
6. Jobling, J. W., and Petersen, W.: The non-specific factors in the treatment of disease, Jour. Am. Med. Assn., 1916, lxvi, 1753–1756.
7. Boas, H., and Ditlevsen, C.: Untersuchungen über Noguchis Luetinreaktion, Arch. f. Dermat. u. Syph., 1913, cxvi, 852–864

THE PROVOCATIVE WASSERMANN TEST IN THE CLINICAL DIAGNOSIS OF SYPHILIS*

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Critical revision of first conceptions has overtaken, one by one, our most cherished diagnostic tests, and placed qualifications upon their usefulness which make their correct interpretation and wide application increasingly difficult. Even so striking and valuable a generalization as that which forms the foundation of the Wassermann test has been subjected to so many readjustments with the advance of knowledge that the clinical syphilographer is at times almost disposed to underrate it. On the other hand, the general diagnostician, hard pressed for a means of rapid decision in a case, frequently overrates it. In particular the negative Wassermann reaction has had to bear the brunt of the assault on the test, and it is probably for this reason that any means of making a negative Wassermann test positive has met with especially enthusiastic acceptance.

The so-called provocative Wassermann test is based upon an observation made by Gennerich in 1910 and confirmed by Milian, to the effect that a syphilitic serum weakly positive or even negative before, can be rendered strongly positive following an injection of salvarsan. Gennerich conceived the reaction to be a phase of the Herxheimer reaction, and ascribed to it considerable value in the detection of latent syphilis, especially in cases in which treatment had been given followed by a rest period. Under the advocacy of Lier, Hoffmann, Lerredde, Fordyce, and other syphilographers of large experience, and following the encouraging reports of Pease and Craig as to its usefulness, the procedure is gaining currency as a method of diagnosis, and as a prerequisite to a decision as to whether or not a patient is to be discharged as cured. A dissenting voice has, however, recently been raised by King, who, in a limited number of cases, could find little evidence of a provocative effect produced by an injection of salvarsan in syphilitics. He pointed out,

moreover, that the work of Boas, and a careful analysis by Haller of the factors of technical error and variations in the reagents used in the Wassermann test, might explain the apparent reversal of reactions under the influence of salvarsan. Haller believes that little variation occurs in the syphilitic serum itself. King proposes as an essential condition of a valid provocative procedure that all the tests, both on blood drawn just before and after injection, should be performed at one sitting with the same reagents, thus reducing to a minimum the factor of technical variation. In estimating the significance of a provocative procedure, attention must also be drawn to the bearing of Craig's work upon Wassermann variations in untreated cases. In a long series of cases under carefully controlled conditions, he found, in seemingly diametric opposition to Haller, that wide fluctuations could occur within a very short time (as short as one day) in the complement fixing power of the serum of a given syphilitic patient. Between the two views there is little recourse to argument, and the presumption is that both factors play a part in actual practice. Craig vigorously advocates the provocative as a diagnostic procedure and a means for controlling the effect of treatment.

It must be conceded that if the provocative procedure is to have any value for diagnostic purposes it must be cleared by painstaking investigation from the charge of being merely a product of technical or fortuitous variations in the behavior of the reagents or of obscure and independent· changes in the patient's serum. The number of provocative reactions thus far reported seems scarcely sufficient to show a degree of uniformity in the production of provocative effects sufficient completely to eliminate the possibility that they occur independently of the injected therapeutic agent. Nor can the Wassermann test itself be regarded as yet as a procedure sufficiently standardized to admit of the searching comparison of the results of different observers. The present study, however, disclosed certain suggestive grounds for believing that the provocative Wassermann test is not merely another example of *post hoc, propter hoc*. Our conclusions are, therefore, carried to completion as if the worth of the test were fully established.

The material here presented consists of 103 cases in which provocative procedures to activate a negative Wassermann were undertaken for purposes of diagnosis. Parallel to this series, through the courtesy of Dr. A. H. Sanford, we were given the opportunity to compare 72

repeated Wassermann reactions, done under conditions similar to those prevailing in the series of provocative tests. The work was not begun with any preconceived aim, but arose out of impressions developed in the course of the routine work of the Section, some of which have been confirmed and others reversed by the study. For that reason certain of the results show a mixture of methods, and represent the average conditions of a clinic rather than an experimentally controlled investigation.

In the provocative procedure, salvarsan or neosalvarsan alone was used, no patients receiving mercury until the procedure was finished. The dosage varied from 0.3 gm. in the earlier cases, to 0.6 gm. neosalvarsan or 0.4 gm. original salvarsan in the later cases. The doses were varied with the conventional contraindications.

The negative Wassermann tests, as a result of which provocative procedures were carried out, were taken at varying intervals before injection, as a rule within a week. It was impossible usually to make repeated tests before injection. In a part of the series the blood to be tested for a provocative effect was drawn on the third or fourth and the seventh days after injection. It had been our practice to perform the Wassermann tests on this blood on different days, thus introducing unintentionally the factor of technical variation to which Boas, King, and others have called attention. When it was definitely decided to make a study of a series, the procedure was modified in a limited number of cases, through the coöperation of Sanford, so that four different antigens were used for a time in the performance of these Wassermann tests, and, so far as possible, the blood drawn just before injection and two or three of the bloods drawn after injection were run on the same day.

The routine Wassermann technic of the Clinic, carried out under the direction of Sanford, employs one Noguchi antigen and a rabbit-human hemolytic system, guinea-pig complement, and fresh, active patient's serum, with the usual controls. When more than one antigen was employed, two alcoholic extracts of syphilitic liver, a stock Noguchi antigen, and an alcoholic antigen, reinforced with 0.4 per cent cholesterin, were employed. Two antigens adapted to other systems but tried out in the laboratory at this time were found to be anticomplementary in the dilutions used and the results discarded, which accounts for the gaps in the four-antigen series (Table 1).

In common with a number of clinicians, one of us (Stokes) had been

'17—38

TABLE 1.—SUMMARY OF FIVE FOUR-ANTIGEN PROVOCATIVE TESTS

	Case 177785				Case 95838				Case 184981				Case 185729				Case 186777			
Presalvarsan Wassermann	2/9/17*				2/27/17				2/9/17				1/23/17				2/27/17			
Provocative injection	2/15/17† Neosalvarsan 5 gm. Intravenously				3/1/17 Neosalvarsan 6 gm. Intravenously				2/10/17 Neosalvarsan 6 gm. Intravenously				2/15/17 Neosalvarsan 6 gm. Intravenously				3/1/17 Old Salvarsan 3 gm. Intravenously			
Antigen	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV
First day	—	—	—	(M)† +++	—	—	—	(M) +++	—	—	—	—	—	—	—	(M) +++	—	—	—	(M) +++
Second day	—	—	—	+++	—	—	—	+++	—	—	—	—	—	—	—	+++			(3)	+
Third day	—	—	—	+++	—	—	—	(M) +++	—	—	(H) +++	(M) +++	—	—	—	—	—	—	(M) +++
Fourth day	—	—	++ §	(M) +++	—	—	—	+++	—	—	+++	(M) +++	—	—	—	(M) +++			(3)	+
Fifth day	—	—	(M) ++	+++	—	—	—	(M) +++	—	—	+++	(M) +++	—	—	—	—	—	—	(M) +++
Sixth day	—	—	—	—	—	—	—	—	—	—	+++	+++	—	—	—	—			(3)	+
Seventh day	—	—	—	—	—	—	—	(M) —	—	—	—	—	—	—	—	(M) —	—	—	(M) +++
Eighth day	—	(H) +++	—	(M) +++									—	—	—	(M) —			(3)	+
Ninth day																				
Tenth day																				
Eleventh day								(M) —				(M) —				(M) —				

*Date of presalvarsan Wassermann. † Provocative injection with date. ‡ The (M) antigen is a cholesterinized alcoholic syphilitic liver antigen.
§ +++ indicates total inhibition.

impressed with the provocative effect upon the Wassermann reaction of a single dose of salvarsan, by a case in private practice in which a Wassermann, frankly negative by one serologist (using five antigens) and faintly positive by another, had become a two plus with one antigen forty-eight hours after injection of 0.3 gm. neosalvarsan, and three plus with two antigens seventy-two hours after injection, the second result being confirmed by a third serologist. The patient gave a positive history, and under treatment became entirely negative. Isolated examples of this type are probably fewer in number than they would be if a strict technic could be followed in all cases. In our experience in this series the reversal of the Wassermann seems to occur rather abruptly in many cases, so that a twenty-four-hour interval in drawing the blood is too long to get the finer gradations in intensity of the reaction which may be shown by very sensitive antigens. On the other hand, our series suggests that some of these finer gradations may be a function either of the technic or of variations in the behavior of the reagents, and for that reason must be interpreted with caution. We desire to add to the criteria already summarized by King the opinion that a careful study of the results obtained by the serologist performing the tests is an integral part of the interpretation. Such an evaluation of the Wassermann furnishes interesting indirect evidence as to the existence or non-existence of provocative effects, even when the test itself as conventionally performed leaves uncertainties which impair its validity.

In estimating the trend of the Wassermann technic in accordance with this belief, we had available, through Sanford, the reports of 72 repeated Wassermann tests in untreated cases, each performed within the average period of time occupied by a provocative procedure and occurring among approximately 6000 tests. These had been requested by clinicians for the confirmation of the first finding, some as a matter of routine and others because the test seemed to conflict with clinical expectation, or, as in latent cases, came as a surprise to the clinician.

Of the 72 repeated tests, 25 (34.7 per cent) showed a reversal of the first finding by the second. Of these reversals, 3 (4.2 per cent) were from negative to positive (in the direction of the provocative) and 22 (30.5 per cent) were from positive to negative (against the provocative), including reversals from weak positive to negative. In other words, the tendency of the Wassermann as carried out in the Clinic was 30 in 100 against the production of provocative effects, as compared with 4

in 100 in the other direction, since in the former percentage of cases the mere repeating of the test was likely to convert even a previous positive into a negative, rather than the reverse.   A variation of this type where a large number of Wassermanns are being performed should be inter-preted as an eminently conservative tendency which results in the production of more negatives than positives in suspected cases.   Prob-ably both factors are concerned, as shown by the analysis of the reversals by days.   It may be stated in general, however, that it is the experience in the Mayo Clinic that the Wassermann as here performed is conserva-tive, and is more likely to return negatives than positives in the face of a reasonable clinical expectation of syphilis.

Of the 25 reversals occurring on 15 pairs of days, 13 (52 per cent) could be grouped as occurring on 4 pairs of days.   The percentage to be expected pro rata in these four days would be only 28.5.   All these reversals were from positive to negative, so that none of them could have played the rôle of positive provocatives.   On one of these days two weak and three strong positives were reversed to negative, and yet in spite of this apparently negative tendency on the second day, one provocative injection fell positive.   On another pair of days, in which three reversals from positive to negative occurred, two provocative in-jections fell negative on the day of supposed negative tendencies.   We were unable to find any evidence that on the days of supposedly positive tendencies a tendency to produce positive provocative results occurred, but on one day of positive tendencies a Wassermann which had been positive three days before was reversed to negative.   It seems evident from these figures that a number of factors are at work, in part inherent in the technic and reagents, as suggested by Haller's and Boas' results, and in part concerned with changes in the patient's serum as suggested by Craig.   It seems fully as apparent that there is a variation in the technic of a competent serologist which must be a factor in provocative procedures undertaken with his coöperation.   For that reason, as already stated, it is imperative, in estimating the value of a provocative, that the trend of the serologist's technic should be thoroughly under-stood.   It is Sanford's intention to do a Wassermann which will, if anything, err in returning negatives in syphilitics rather than positives in non-syphilitics; and his use of the less highly fortified antigens, the general experience of the Clinic with the Wassermann performed in his laboratories, together with the results of the examination described here, all entitle his technic to be regarded as conservative.   The value

of a reversal from negative to positive under a provocative procedure done with his coöperation is, therefore, entitled to correspondingly greater weight.

DIRECT EXAMINATION OF THE PROVOCATIVE PROCEDURE

Our efforts to satisfy ourselves of the existence of such a change in complement-fixing power as the positive provocative Wassermann represents have not been entirely satisfactory, in that our conception of what constitutes rigid criteria was not reached until a number of results had accumulated, and the effort to try out the effect of a number of antigens and daily tests on the procedure overtaxed our facilities so that some confusion and partial results ensued. The occasions on which blood was drawn and tested just before the salvarsan was given and for several days after all happened to be negative provocative tests, the results before and after salvarsan agreeing in being negative to all antigens used, when done on the same day. We are, therefore, left with the perplexing feeling that while there may be a provocative effect, and that a variety of considerations point to it, we have been unable to prove its existence beyond doubt with the facilities at our command. The demonstration of the value of the test can be made only by the use of methods which would be too elaborate to be applicable to average clinical conditions considering the amount of information which the test is likely to supply for purposes of diagnosis. The chief particular in which our more carefully worked-out positive results do not conform to the strictest requirement is that pointed out by King, that the blood drawn just before salvarsan should be examined at the same time and with the same reagents as the blood drawn after it. Nevertheless, the five positive provocative tests represented in Table I are suggestive. The patient (Case 184981) in particular exhibited, in addition to his serologic changes, a local Herxheimer reaction in the grouped follicular recurrent syphilid of the buttock which he presented at the time of his examination. The lesions then healed, leaving scars. He gave a history of a genital lesion fourteen years before; no secondaries were observed and local treatment only was given. The remaining patients, except one, presented suspicious histories or findings which were not clear cut.

CASE 177785.—Diagnosed clinically as pernicious anemia. Atypical as to blood findings and with central nervous system changes which suggested early tabes. He had given a weak positive Wassermann five weeks before the provocative, and a negative seven days before injection. The provocative effect outlined in the chart was followed by a

negative six weeks later. A striking subjective improvement occurred, but should be interpreted with caution since only salvarsan was used, and the effect may have been due entirely to arsenic.

CASE 95838.—The wife of a syphilitic patient, anemic and below par. Husband with positive Wassermann had married her two years after an untreated infection. Aphonia lasting some weeks. Two negative Wassermanns on previous occasions. Provocative effect followed by a complete negative on the ninth day, with a striking improvement under mercury.

CASE 183729.—Diplopia with right external rectus paralysis. History of gonorrhea from first husband. Two years later, transient diplopia; no symptoms during intervening time. Five years previously diplopia and strabismus reappeared and have been permanent; no other explanation than lues apparent. Spinal puncture not obtained. Nothing else on which to base a diagnosis of syphilis. The patient was negative as late as the tenth day after the one-antigen positives on the first and third days. No change under therapy. Clinically we regard this case as unconfirmed, though suspicious.

CASE 186777.—Definite history of old infection, with much treatment. Mental condition suggested an early paresis, but the neurologic findings were too indefinite on which to base a diagnosis. Puncture refused. No therapeutic test.

The antigen responsible for the majority of the positives above described was a cholesterinized alcoholic syphilitic liver antigen. This antigen, together with one of the stock acetone-insoluble fraction antigens of the laboratory, had proved very sensitive in picking out suspicious cases which were negative to the ordinary technic. It remains a question in our minds, however, whether the possibility of false positives as suggested by such cases as No. 183729 is not too serious to discourage the interpretation of a positive with only one antigen in four as evidence of syphilis.

In only one of our series of nineteen positive provocatives done with one antigen was there any evidence of a gradual increase in the strength of the complement-fixing power of the serum, as evidenced by a weak, followed by a strong, positive after salvarsan. In this case (Case 177564), a woman with gastric crises, a negative test four days before salvarsan was changed to a weak positive three days after, followed by a strong positive on the seventh day. Another patient (Case 179741) with early tabes and a history of five injections of salvarsan and ten of a mercurial salt intramuscularly was negative eight days before injection, weak positive on the sixth day after, and again negative on the ninth day. Cases of this type are merely suggestive, not conclusive, and, as has been

previously pointed out, form the basis for the doubts expressed as to the existence of a provocative effect because of their known occurrence under other circumstances. We feel, however, that the conservative tendency of the technic employed, as evidenced in our comparative figures, entitles such data to consideration in weighing the probabilities.

We believe that our direct data, as presented herein, while not absolutely conclusive, offer strong presumptive evidence that a change in the complement-binding power of negative syphilitic serums can be secured in a certain percentage of cases by the administration of an abrupt therapeutic shock, so to speak, in the form of an injection of salvarsan. The mechanism of such an effect can, in the present state of our knowledge of the immunology of syphilis, be regarded only as a matter for conjecture.

Granted, then, for the time being, that a provocative effect exists, the following results may be presented as indicating the place which such a procedure should hold in the diagnosis of obscure syphilis. In considering the available material, data were gathered on relation of the provocative to clinical signs of syphilis, to the history of the disease, to the stage and type of syphilis, on the confirmation of the provocative test by the therapeutic test, and on the comparative value of the latter as a means of recognizing suspected cases. In estimating the efficiency of therapeutic tests, a liberal allowance was made for the recognized tonic effects of an arsenical preparation such as salvarsan, especially in conditions like suspected pernicious anemia and the tuberculids, in which arsenic is known to be of value. It may not be out of place to state that for us a therapeutic test does not mean the administration of iodids, or the desultory or inefficient use of mercurials. Our average therapeutic test includes three weeks of vigorous mercurialization with weekly injections of salvarsan if not contraindicated, the administration of the mercury being intramuscular, usually as a soluble salt, or by the vigorous use of inunctions.

The Positive Provocative Test

Of 103 provocative tests, 19 (18.4 per cent) showed a reversal of the Wassermann from negative to positive. This finding should be considered in the light of the comparisons with the repeated Wassermanns, in which it was suggested that the tendency of the technic to turn negatives into positives, unaided by a provocative injection, was only 4.2 per cent. If an injection of salvarsan can convert a 30.5 per cent tendency against a positive into an 18.4 per cent tendency in

favor of a positive, it would seem to have a place as a diagnostic proce-
dure.

Of the cases showing positive provocative tests, 26.3 per cent pre-
sented no objective clinical signs calculated to arouse the suspicion that
the patient was syphilitic. Of the positive provocative cases, 73.7 per
cent of the patients showed clinical signs which could be regarded as
suspicious.   In no one of the positive cases were the signs so indubitable
that the provocative could be regarded as unnecessary or merely con-
firmatory.   Typical examples of such groups of symptoms are found in
sluggish pupils and indefinite gastric symptoms in the absence of definite
stomach findings; periostitis of the sternum with enlargement of the
liver, aphonia with slight anemia, etc.

A definite history of syphilis, interpreted to mean a reasonably clear
account of primary and secondary manifestations, was given in 57.8
per cent of the positive provocative cases.   Suspicious histories, such as
miscarriages, infected husband, etc., were given in 31.5 per cent.   No
history whatever could be elicited in 10.7 per cent. In no instance was a
provocative undertaken in the absence of both history and clinical signs.

The duration of infection ranged from one to eighteen years, with an
average of ten years.   Two provocative tests were positive in patients
giving a definite history of well-treated infection, but no signs where the
test was intended to determine the need for further therapy.   Since this
constitutes a positive result in one-third of the cases in which we used
the provocative procedure for this purpose, we believe the test has
distinct value in determining the status of a patient under treatment.
The Wassermann histories in general were unsatisfactory.   Four pa-
tients who gave histories of having previously been positive elsewhere
became positive again after a negative in this Clinic.

The therapeutic test yielded figures of special interest, which it is
our purpose to emphasize.   Of the total number showing positive pro-
vocative effects, the therapeutic test confirmed the serologic finding in
60 per cent of 15 patients that were treated.   In 40 per cent the thera-
peutic was rated as doubtful or negative (6.7 per cent) and contributed
nothing further to the diagnosis.   The doubtful therapeutic tests in-
cluded such cases as one patient with possible syphilitic anemia simu-
lating pernicious anemia, treated with salvarsan, one with a history and
previous antisyphilitic treatment but no signs, two undoubted syphilitics,
one of whom had had so much recent treatment that little effect was to
be expected, and the other so late and unfavorable that not much could
be accomplished.

Previous treatment had been administered in 45 per cent of the patients showing a provocative effect, and 55 per cent had had no treatment. Two patients had been taking pills practically until their arrival. Of five who had had a fair combined treatment with mercury and salvarsan, three (60 per cent) were recognized only by the more sensitive antigens used. Two of these three were clinically suspicious, however, at the time. ·

The cases showing positive provocative effects were distributed as follows: Syphilis of the mucous membranes (late), 4 cases; of the skin, 3 cases; of the osseous system, 1; of the central nervous system, 3; of the vascular system, 1; latent cases, 4; type uncertain, 3.

THE NEGATIVE PROVOCATIVE TEST

Of the 103 provocative tests performed, 84 (81.6 per cent) showed no change in the negative Wassermann as the result of an injection of salvarsan. Of these 84 cases, 32.2 per cent were clinically negative, and 67.8 per cent clinically suspicious. It will be noticed that the tendency to a negative provocative is paralleled by fewer evidences of syphilis. Only 17.2 per cent of patients with negative provocatives gave definite histories of primary and secondary manifestations as compared with 57.8 per cent among the positive cases. In 52.6 per cent suspicious histories were obtained, a slightly larger proportion than among the positive cases. No suggestive history could be given by 30.2 per cent as compared with 10.7 per cent among the positive cases. The greater indefiniteness of history and findings in the negative group, to be expected under the circumstances, is apparent.

The therapeutic test again affords interesting figures. Twenty-three patients received the benefit of a therapeutic test, and of this number, in spite of the failure of the provocative injection to reverse the negative Wassermann, 65.2 per cent showed improvement striking enough to clinch the diagnosis. This parallels the 60 per cent among the positive provocative cases, but is more significant because it made, instead of merely confirming, the diagnosis. In 34.8 per cent the negative result of the provocative test was confirmed by the absence of improvement under therapy. The therapeutic test was rated as doubtful in 13.3 per cent of the total number of negative provocative tests performed. A therapeutic test was advised in 43 and carried out in 23, or 53.5 per cent. In 51.2 per cent of the patients giving a negative result on provocative injection, the result was accepted as eliminating the possibility of syphilis in conjunction with the lack of definite findings.

Cases of this type included histories of sexual exposure with neurotic and syphilophobic symptoms; selected cases of obscure arthritic manifestations without other evidence of syphilis; cases of epilepsy with one or two suggestive points in the family history, but no stigmas; cases with histories of a previous positive Wassermann from unreliable source, without adequate clinical reason for suspecting syphilis; mental deviates and constitutionally subnormal persons presenting no definite stigmas of heredosyphilis; patients with perforated nasal septum, with backache and negative x-ray; women with a series of miscarriages without other evidence of syphilis in history or examination; husbands or wives whose partners were syphilitic but who themselves presented no signs of the disease.

It is, of course, impossible to fit all types of cases into one rule in deciding the finality of a negative provocative procedure. It should be recalled that our fully developed technic called for five Wassermann tests over a period of from seven to ten days, so that in no case was a single negative accepted as evidence of the absence of syphilis. In many of the negative cases in which no therapeutic test was indicated, the patients were advised to repeat the Wassermann at the end of three months or more.

The cases in which no provocative effect could be secured included 1 of late syphilis of the mucous membranes, 2 of cutaneous late syphilis, 4 of osseous syphilis, 9 of central nervous system involvement, 2 of vascular syphilis, two of heredosyphilis, 6 latent cases, and 58 which could be rated as so doubtful that a diagnosis of syphilis could not have been made without a positive Wassermann reaction. In only 13 per cent of the negative cases after a general examination did we feel that the diagnosis could be made clinically and that the provocative procedure requested by the general clinician was merely confirmatory.

COMBINED RESULTS

Summarizing the results for our entire series, we find that 69 per cent, or more than two-thirds of patients on whom provocative procedures were undertaken, showed clinically suspicious signs of syphilis. A fourth of them (25.2 per cent) gave definite histories of primary and secondary lesions, half of them (48.4 per cent) presented suspicious facts in their histories, and the remaining fourth (26.4 per cent) could give no significant history. Two-thirds (63.1 per cent) of those treated (38 in 103) had their diagnosis made or confirmed by a therapeutic test, and two-thirds of these were from among those whose provocative test was

negative, making therapy the last diagnostic resort (excluding in a small percentage the possible results of lumbar puncture).   Three-fourths of all the cases on which we had data (76) had been treated, one-fourth had not.   The percentage of cases previously treated was, if anything, a little higher among those showing positive provocative effects than among those showing negative results (44.5 per cent as against 32.8 per cent) (Table 2).

TABLE 2.—SUMMARY OF CLINICAL RESULTS

	Clinically Suspicious, Per Cent	Clinically Negative, Per Cent	Definite History, Per Cent	Suspicious History, Per Cent	Negative History, Per Cent	Positive Therapy, Per Cent	Negative Therapy, Per Cent	Doubtful Therapy, Per Cent	Previous Treatment, Per Cent	No Previous Treatment, Per Cent
Positive provocative effect	73.7	26.3	57.8	31.5	10.7	60.0	6.7	33.3	44.5	55.5
Negative provocative effect	67.8	32.2	17.2	52.6	30.2	65.2	34.8	...	32.8	67.2
Combined results	68.9	31.1	25.2	48.4	26.4	63.1	23.6	13.3	39.4	60.6
Total number of cases	103			95			38		76	

With reference to the value of the provocative procedure in different types of syphilitic manifestations, Table 3 summarizes the results of our series.

TABLE 3.—EFFICIENCY OF THE PROVOCATIVE TEST IN VARIOUS TYPES OF SYPHILIS

Type	Number of Cases	Percentage Positive
Heredosyphilis	2	0
Osseous	5	20
Central nervous system	12	25
Vascular	3	33
Latent	10	40
Late cutaneous	5	60
Late mucous membrane	5	80

Combining certain of these results, it appears that in only 27 per cent of cases is the provocative procedure likely to be of use in identifying active deep-seated visceral, osseous, or central nervous system syphilis. Its efficiency rises to 40 per cent in latent cases, and to 70 per cent in late cutaneous and mucous membrane syphilis.   It is in precisely these last-mentioned types of syphilis that it is least likely to be of use, since the diagnosis can usually be made by a syphilologist from the morphology of the lesion.   It appears, therefore, from our series, that the re-

activation of a negative blood Wassermann for purposes of diagnosis is least valuable precisely where it is most needed; that is, in obscure visceral, osseous, and central nervous system syphilis.   The number of cases is, of course, too small for final conclusions.   We are unable to estimate accurately the possibility of false provocative results, since in three doubtful cases with positive results strong clinical ground still existed for suspecting syphilis, although the cases had to be left indeterminate.

DISCUSSION OF RESULTS

From our study of the provocative effect upon the Wassermann test in clinical application, we feel that complete proof of the existence of such a reaction will be available only when the following technic has been carried out in a number of cases.   Blood should be drawn at more frequent intervals than twenty-four hours—perhaps as often as once in three or four hours—and one-half of it held in reserve to be done at a single sitting while the other half is examined day by day.   Several antigens should be used, and these antigens and the other reagents employed should, so far as possible, be kept constant throughout the tests. A series of bloods should be examined before the provocative injection is given in order to ascertain, if possible, the normal behavior of the serum to be examined for provocative effects.

We have not been impressed with the necessity for continuing the examination of the blood after a provocative injection beyond the tenth day.   If possible, two serologists should work together, using the same reagents to determine the personal equation in the reaction.   It is only necessary to total the figures for the number of single-antigen Wassermanns which would have to be done to satisfy these none too exacting requirements, to realize that the provocative Wassermann reaction will not soon rest upon an uncriticizable foundation.*   We had abundant

* Six bloods drawn in twenty-four hours on each
   case for three days...................... 18 single-antigen Wassermann tests
Two bloods drawn each twenty-four hours on
   each case for seven days................ 14   "   "   "   "

    Total............................. 32   "   "   "   "

Dividing the blood for final and daily study ... 64   "   "   "   "
Dividing each blood between two serologists .. 128   "   "   "   "
Four antigens used on each case............ 512   "   "   "   "

    Total............................. 704   "   "   "   "

Our experience indicates that one case in five will furnish a positive effect. The investigator may, therefore, unless fortune favors him, have to provide for 2560 single-antigen tests before securing one provocative effect completely worked out.   This takes no account of the Wassermanns that should be done on the serum before provocative injections.

reason to appreciate the almost insurmountable difficulties in the way of an absolutely controlled procedure in the course of our own work.

The precise nature of the provocative effect, if such exists, could not be determined from our studies. We feel that there is reason to doubt whether it is comparable to the clinical Jarisch-Herxheimer reaction as suggested by our patient (Case 184981). Several of our patients who remained negative on the blood showed a symptomatic Herxheimer reaction. This was especially marked in patients with syphilitic periostitis, in which, after a marked exacerbation, the pain promptly disappeared. A local Herxheimer reaction was especially conspicuous in a periostitis of the upper third of the sternum (Case 185869) which, nevertheless, remained Wassermann negative, and cleared up subsequently under mercury and iodids.

We were, in fact, impressed on several occasions with the value of the Herxheimer reaction as a corroborative sign, even when the provocative procedure had failed, and considered it an indication for a therapeutic test. Unfortunately, exact notes were not kept on this point, so that an estimate of its value will have to be deferred to a later study. Its value in syphilitic periostitis has been herein noted.

The most interesting and suggestive result of the entire study to us was the demonstration of the efficiency of the properly performed therapeutic test as a means of diagnosis in obscure syphilis, and its obvious superiority to the provocative procedure. We were also impressed by the parallelism between the percentage of patients who were clinically suspicious of syphilis (68.9 per cent) and the percentage proved to be syphilitic by an effective therapeutic test (63.1 per cent). It seems from these figures, as well as from the failure to secure provocative effects among cases in which there was serious doubt of the existence of an infection, that clinical signs are the basic fact in the diagnosis of syphilis. Their confirmation by therapeutic test was, in our series, greatly superior to an effort at diagnosis by provocative procedure. The efficiency of the provocative test in our series is approximately 18 per cent; that of the therapeutic test in the cases on which it was tried was 60 per cent—a difference amounting to 42 more chances in one hundred of clinching the diagnosis by therapy than by provocative. From our study of this series we should rate a thoroughgoing clinical examination first as a means of disclosing the presence of syphilis. A strong suspicion on examination, unconfirmed by Wassermann, will have 18 per cent further prospect of confirmation by provocative, and the

following of the negative provocative by a therapeutic test will give at least an additional 42 per cent prospect of identifying the trouble. Emphasis should be laid on the meaning of a clinical examination, which should include a carefully taken history and the study of the patient, at least from the point of view of the internist, the dermatologist, the ophthalmologist, the neurologist, and the otolaryngologist before a final decision is reached.

In the foregoing presentation we have indicated in a negative way, rather than a positive, what we regard as the indications for a provocative test and for subsequent application of a therapeutic test, by detailing the types of cases which were clinically doubtful with negative provocative tests. In general it may safely be said that the provocative should not become a routine accessory of the negative Wassermann reaction in the absence of good clinical ground for suspecting syphilis, since the percentage of positives in such cases seems to be so small as not to justify the procedure.

While it is impossible to lay down the indications for a provocative procedure, and its limitations in cases in which it is most needed have been suggested in our results, we are accustomed to regard the following as indications, in addition to the more obviously clinical symptoms of the disease when occurring with a negative Wassermann:

1. A definite history of primary or secondary lesions or a suspicious genital sore of any description.

2. Syphilis in husband or wife or a history of a sore in either.

3. Treated cases to determine the fact of cure or need for further treatment. One-third of the cases thus tested by us gave a positive provocative effect.

4. Obscure bone and joint lesions.

5. Histories of miscarriages unless the anatomic cause is glaringly obvious.

6. Mothers of syphilitic children without clinical signs of the disease.

7. Cases with a history of a positive Wassermann elsewhere, negative on present examination.

8. Mental deviates and constitutionally inferior persons with suspicious histories.

9. Certain signs elicited by the special examinations, such as decreased bone conduction with normal hearing, chorioretinitis, and retinitis pigmentosa, bilateral dacryocystitis in childhood, etc.

The technic of the provocative test, in our opinion, should include

in practice a Wassermann with several antigens done on blood drawn
at the time of injection, and on blood drawn daily thereafter for one
week.   It is desirable that all these bloods be tested at one sitting, with
the same reagents.   This procedure is a serious tax on average clinical
laboratory facilities, but we believe it offers the maximum prospect of
success within the limits of clinical applicability.   With the use of mer-
cury intramuscularly as a provocative agent we have had relatively
little experience, although we have seen occasionally apparently posi-
tive provocative effects secured by it.   In a large clinic with a special
service for syphilis the salvarsan provocative is so much more expe-
ditious and compact a procedure that it would seem the method of
election wherever it can be used.

It is not our purpose in this paper to consider the technic and clinical
applicability of the therapeutic test for diagnosis and the indications for
its use further than to say that it should be conducted with vigor, tem-
pered by good judgment, and not consist of iodids and pills.   We are
inclined to believe, from our experience with it thus far, that if it can be
applied with the requisite judgment to properly selected cases, it is so
much more valuable than the provocative procedure that it should take
precedence over it if a choice is necessary, and should follow it if the re-
sult of the provocative test is negative and the clinical suspicion strong.

SUMMARY

1. From a study of 103 cases in which an injection of salvarsan was
given to provoke a positive Wassermann after a negative test, presump-
tive, but not conclusive, evidence of the existence of a provocative effect
was obtained.

2. A knowledge of the tendencies and limitations of the Wassermann
technic employed should form a part of any study of the clinical value
and interpretation of the provocative Wassermann test.

3. Such a study on a series of repeated Wassermann tests in the
Mayo Clinic seemed to indicate that the tendency of the technic was
conservative and against the conversion of negative into positive re-
action without the administration of salvarsan.

4. It seems probable that both individual technical variations and
variations in the reagents are a factor in the results in addition to the
provocative effect.

5. Positive provocative effects were obtained in 18.4 per cent of 103
cases.

6. The provocative test was of value in recognizing as insufficiently treated two out of six cases (33.3 per cent) in which it was applied to determine whether a cure had been attained.

7. A strictly controlled and completely worked-out provocative procedure involves an amount of labor which makes it clinically inapplicable, and it seems probable that this same obstacle will keep it in the field of presumptive rather than conclusively demonstrated clinical phenomena for some time to come.

8. The provocative test in our series seemed to be of the least service in active deep-seated visceral, osseous, and central nervous system syphilis, where it was most needed, fairly efficient (40 per cent) in latent syphilis, and most often positive in late cutaneous and mucous membrane manifestations, where the diagnosis can often be made morphologically.

9. Our results do not suggest that the provocative is entirely a Herxheimer reaction phenomenon, since local and symptomatic Herxheimer reactions occurred in our series in cases in which no provocative effect could be recognized, as well as in cases showing a provocative effect. It is possible, however, that the use of several very sensitive antigens might demonstrate an effect not detected in routine procedure.

10. A suggested procedure for provocative tests is given elsewhere in this article and seems to us to represent a compromise between the clinical impossibility of a fully controlled procedure, on the one hand, and partial and untrustworthy methods, on the other. At its best the test yields a rather small return for the amount of trouble, and if overelaborate, is subject to the same risk of error as the oversensitive Wassermann test.

11. Certain special indications for the provocative procedure are enumerated elsewhere in this article.

12. The percentage of patients whose syphilis was suspected from clinical examination ran parallel to the percentage shown to be syphilitic by therapeutic test, and far in advance of the number shown to be syphilitic by the provocative test.

13. The therapeutic test, properly applied to suitable cases, would seem to be of more value in clinical diagnosis of obscure syphilis than the provocative Wassermann test.

14. Positive therapeutic effects were obtained in 63.1 per cent of 38 cases, and in 65.2 per cent of 23 cases in which the provocative test had failed to establish the presence of syphilis.

15. The provocative Wassermann would seem to be of little value in the absence of clinical evidence of the disease, and to be inferior both to clinical judgment and the therapeutic test in the recognition of obscure cases.

REFERENCES

Boas, H.: Quoted by King.

Craig, C. F.: Variations in the strength of the Wassermann reaction in untreated syphilitic infections, Jour. Am. Med. Assn., 1914, lxii, 1232–1236.

Craig, C. F.: The results and interpretation of the Wassermann test, Am. Jour. Med. Sc., 1915, cxlix, 41–56.

Fordyce, J. A.: The diagnosis and general treatment of syphilis, Am. Jour. Med. Sc., 1916, clii, 469–489.

Gennerich: Ueber Syphilisbehandlung mit Ehrlich 606, Berl. klin. Wchnschr., 1910, lxvii, 1735–1742.

Haller, D. A.: Variations in the strength of positive Wassermann reactions in cases of untreated syphilis, Jour. Am. Med. Assn., 1916, lxvi, 882–887.

Hoffmann, E.: Der Wert des Salvarsans für die Abortivheilung der Syphilis, Deutsch. med. Wchnschr., 1914, xl, 1168–1170.

King, J. T., Jr.: The quantitative effect of salvarsan on the Wassermann of the blood, Jour. Am. Med. Assn., 1916, lxvii, 1669–1671.

Lier, W.: Ueber Abortivkur, Spirochätenreste und kombinierte Behandlung der Syphilis, München. med. Wchnschr., 1914, lxi, 2233–2236.

Lerredde: Technik der Sterilisation der Syphilis durch das Salvarsan, München. med. Wchnschr., 1914, lxi, 533–535.

Milian: Quoted by Craig.

Pease, M. C., Jr.: The provocative Wassermann reaction, Med. Rec., 1914, lxxxv, 982–984.

'17—39

CERTAIN TECHNICAL REFINEMENTS IN METHODS OF INTRAVENOUS INJECTION*

J. H. STOKES

The administration of salvarsan does not ordinarily appeal to practitioners as an affair of special technical detail, and, as ordinarily performed, it probably does not answer to that description. It was, therefore, with considerable interest that I heard one of the speakers at the recent meeting of the Public Health Administration Section of the American Public Health Association comment on the effect which multiple punctures, incisions, infiltrated arms, and other accompaniments of an unsuccessful and amateurish intravenous technic have on patients for whose treatment repeated salvarsan injections constitute a desideratum from both the medical and social standpoints. I, myself, have been impressed from time to time with the undesirableness, from the technical standpoint alone, of committing to the care of inexperienced interns, house physicians, and practitioners, the salvarsan therapy of syphilis. Even the poor can scarcely be expected to submit with good grace to repeated barbarities offered in the name of medicine. In easy cases almost any technic suffices. But in difficult cases, to give injection after injection into a single available vein concealed below a cushion of fat, without resorting to incision to reach it, becomes a technical accomplishment of no small magnitude.

On my own service there has been gradually worked out a technic which, in our hands at least, has greatly reduced the percentage of technical error. The requirements of this service from the standpoint of technical ability are high, since the clientele consists of pay patients of at least average intelligence, and with quite definite conceptions of the type of service they should receive from a specialist. About four thousand injections of salvarsan are now being given yearly, which makes the pressure of the work such that the technic must be, not only smooth, but rapid, and yet free from slap-dash and short-cuts for the sake of

speed. The technic here described seems to have the advantage that it can be rapidly acquired by a relatively inexperienced operator, and, while it is definite, it is reasonably elastic and adaptable to the variety of conditions met in intravenous work. Injections are given by the chief and the first assistant, although other medical members of the staff may witness the procedure and learn the method on occasional easy arms. It is its applicability to difficult cases which seems to justify the description. The general principles governing this part of the work are as follows:

No salvarsan is given to ambulatory patients. Each must remain under observation in the hospital for at least twenty-four hours. From 60 to 80 per cent of our injections have been of original salvarsan or arsenobenzol, and the balance of neosalvarsan. Strict asepsis is part of the operating-room technic, and the reagents used in the preparation of the drug conform to the original Ehrlich criteria or standard modifications.

Water redistilled from pyrex and Jena glass and boiled is used in all injections. Neosalvarsan is given by the Ravaut method, slightly modified, each decigram of salvarsan being dissolved in 1 c.c. of water, and the dose administered with a Luer syringe. Salvarsan is administered by gravity flow, a concentrated solution containing from four to eight doses being prepared (0.6 gm. in 25 c.c. of the water), and diluted after neutralization and before using, so that 0.6 gm. of the drug is contained in 100 c.c. of the solution. A single graduated container is used, which is suspended from a standard where it is kept throughout the morning's work. Before beginning, the tubing of the container is filled with distilled water to exclude air, but this water is allowed to escape before the first injection is given, so that only salvarsan enters the veins. The glassware is boiled in distilled water. The needles and the salvarsan ampules are sterilized in 95 per cent phenol, followed by alcohol, and the needles are rinsed in redistilled boiled water, in order to avoid the use of disinfectants containing metallic salts, such as bichlorid. Gloves are sterilized by boiling and are put on dry.

The indications and contraindications for the use of salvarsan and neosalvarsan need not be discussed in a technical paper further than to say that in my experience the effort to reduce the technical difficulties of the administration of original salvarsan by the use of concentrated solutions, as recommended by Brayton (Jour. Am. Med. Assn., 1916, lxvi, 1921–1922), has not been entirely satisfactory for general use. It

is valuable when one or two injections must be given unaided, but with the assistance of even an amateur or an office girl it is unnecessary. Even with the most careful neutralization, the drug seems to be distinctly irritating, and its injection, especially if the solution is at all hot, may cause collapse. The injection must be made very slowly indeed in large veins, and in small veins there may be intense pain and subsequent thrombosis without subcutaneous infiltration. The method seems to be unsuitable on this account precisely where the technical difficulties are greatest—in wrist and hand veins, and where only one or two unsatisfactory veins are available for a series of injections. The technic to be described has been used on my service in administering amounts of solution up to 100 c.c. with a large Luer syringe, so that concentrated solutions have been discarded entirely in the case of original salvarsan, and there seems to be no difficulty in meeting the indication both in children and adults.

The duties of a nurse or assistant are confined to unsterile manipulations to which even the inexperienced may be easily trained. These manipulations consist in preparing the patient, managing the tourniquet, releasing and closing the tube-clamp in the case of original salvarsan, and pressing a sterile sponge over the point where the needle enters the vein at the time the needle is withdrawn, and then bandaging the arm. The only manipulation calling for any skill is the application of the tourniquet. The preparation of the patient includes the following:

A light breakfast is eaten (tea and toast); the temperature, pulse, and respiration are taken before the patient enters the operating room. The left arm, preferably, is prepared with tincture of iodin, which is then partly washed off with alcohol, so that the color does not conceal difficult veins and so that dermatitis may not ensue. In very difficult arms an alcohol compress may be used after soap and water cleansing. The arm and shoulder should be bare and the neck uncovered, since the slightest constriction may hold the drug in the vein and favor thrombosis. A marked constriction concealed by the shirt sleeve may cause a leakage around the large needle.

One of the seemingly trivial elements in the giving of an injection, but one which should be rated very high, is the confidence and coöperation of the patient. Operating under a general anesthetic, or under a local anesthetic, one seldom realizes the psychic effect on the operator of a nervous or distrustful patient. Panic may seize even the fairly experienced if the goal is not reached on the first attempt; the tense atti-

tude, the shrinking away, the sounds of remonstrance and disapproval from the patient, are only too efficient in bringing beads of sweat to the operator's forehead and in damaging the fine movements of the hands on which his success depends. To stop to cool off may only make matters worse, and to fail entirely is to damage his nerve in subsequent work more seriously than is realized. For these reasons I insist that the atmosphere of the operating room shall be as carefully prepared as that of a social salon. The new, nervous patient having already met the chief

Fig. 256.—Correct positions of operator, nurse, and patient. Schreiber needle technic (original salvarsan).

and his first assistant, is relieved of anxiety as to who is to treat him. He, or more often she, is met with smiles and addressed by name. They are treated as friends from the moment they enter the office and the operating room. They find themselves on the table in a current of casual conversation, good humor, and friendliness which relieves anxiety. Other patients who may have been spoken to have conceded that it doesn't hurt. We do not use large needles without preparing for them by local anesthesia, in which we can use the finest hypodermic needle. I am

firmly convinced that anoci-association, which, after all, is simply a putting of one's self in the patient's place, is an essential ingredient of a technic which is to work day in and day out without a hitch.   Patients who have never been either hurt or scared approach one with the calm-inducing lack of fear with which animals that have never seen man disarm their human enemies.

Lighting.—The operating room should, if possible, be so arranged that the arm is cross-lighted rather than longitudinally or from above, since with the latter illumination especially, the elevation of the skin caused by the vein casts no shadow and is correspondingly difficult to

Fig. 257.—Bedside table used as a very satisfactory rest for the arm.

see.   Light containing much yellow or green, whether from walls, artificial lighting, or shades, may conceal an otherwise visible vein.

Patient.—The patient lies on the table, arm extended at full length at right angles to the body and resting with the palm of the hand on the slanting bedside table which I have adapted to this purpose (Figs. 256 and 257).   This is a strategic position for the administration of an intravenous injection.   The patient is at rest.   The full arm is extended for a survey of the situation.   The carotid and jugular pulsation, the larynx and conjunctiva, and the upper thorax are all in the line of vision, so that the operator himself can follow every change heralding an acute reaction—the acceleration in pulse, the slight uneasiness, the gulp, the sudden catch in the breath, the flush beginning at the clavicle and running

upward, and the engorgement of the conjunctiva. It is impossible for him, without wilful neglect, to continue an injection until he discovers, as he rises and secures a full view of the face at the end of it, that the patient is rapidly becoming livid and pulseless.

Tourniquet.—It is my practice to use a soft band tourniquet, made by folding double a three-inch rubber Esmarch bandage. Thirty inches is an average length. It is used unsterile by the nurse or assistant, who should be taught the following points:

Fig. 258.—Correct application of the band tourniquet to the left arm (Esmarch bandage). The nurse stands at the patient's left shoulder. The tourniquet is pressed downward by the hands, instead of exerting traction.

1. To apply it flat, wrapping and not twisting it around the arm. The two ends pass each other on the flat, so that the effect is that of a

a   b   c   a   b
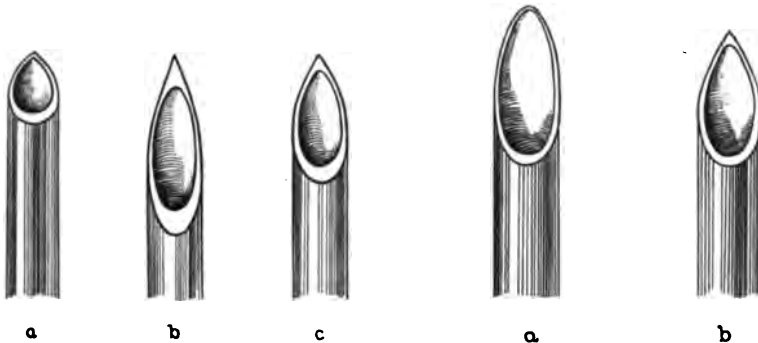
Fig. 259.—Three types of needle point: a, Too short; b, too long; c, correct.
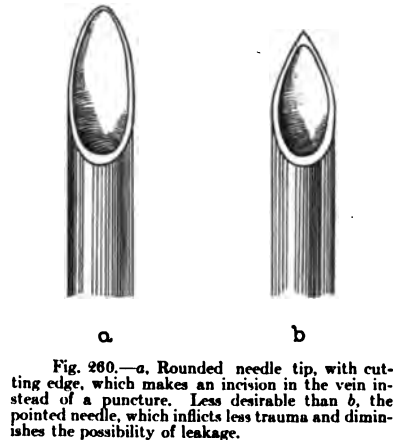
Fig. 260.—a, Rounded needle tip, with cutting edge, which makes an incision in the vein instead of a puncture. Less desirable than b, the pointed needle, which inflicts less trauma and diminishes the possibility of leakage.

cuff rather than a cord (Fig. 258). This minimizes the discomfort to the patient, and promotes the maximum of surface compression with the least compression of the deeper arterial supply. It also prevents the

escape of the vein to be injected under the crossing of the two ends, which occasionally results in the imperfect distention of difficult veins.

2. Two hands should be used in holding the tourniquet, and the release should be without twist or jar, and without unsterilizing the field.

3. The skin should not be pulled aside or twisted on the arm in applying, since the effect is to flatten the vein and render it less palpable and visible.

The Vein.—Certain seemingly obvious details are easily overlooked. A survey of the situation before rather than after an attempt at puncture is essential. In the difficult arm I am inclined to rate palpation above inspection, and for that purpose a single finger should be trained to the acme of tactile acuteness by constant practice. The ball of the middle finger of the left hand is especially serviceable because it has not been rendered insensitive by the trauma to which the other fingers are subject. Cross stroking with this trained finger will detect a deep vein where nothing is visible. By light palpatory downward pressure its caliber and fixation may be estimated. Thrombosis from a previous injection not infrequently is to be detected before entry only by palpation, since the vein may remain of the same caliber at the site of thrombosis as in the

Fig. 261.—Illustrating the effect of partial puncture of a vein, with a long-bevel needle: *a*, Return of blood without completely entering the vein; *b*, infiltration of the subcutaneous tissue even after a return of blood has been secured, as soon as injection is begun.

normal portion. A vein which is not sclerotic and yet rolls sharply under the finger is very apt to be thrombosed.

A variety of devices can be employed to distend difficult veins in addition to the customary clinching of the fist. The most easily available is the slapping of the skin over and around the vein with the flats of the fingers producing a temporary paralysis of the vein wall. This is of so much assistance that I employ it as a routine, since a well-distended vein is better fixed than one less distended. A sharply slanting support sometimes assists in securing an effect. Hot applications are of great value in difficult cases, but are time-consuming unless the patient has been told to soak his arm before coming to the operating-room. This method is also useful in distending small scalp veins.*

* My attention has been called by Dr. Jay Frank Schamberg to the value of daily gymnastics in developing previously small arm veins.

The angle of the vein should be carefully estimated and the depth considered before a puncture is made, especially when the needle is to be advanced well beyond the point of puncture, as in the technic here described. Veins in obese women which show as faint bluish patches at the flexure are apt to be more superficial than one is led to expect, and are likely to be transfixed by overenergetic or jerky operators. The fixation of veins in the connective tissue is a more important factor at times than their caliber, and the thickness and toughness of the skin over a vein is equally important. For example, it is often easier to enter a small, well-fixed superficial vein at the flexure of the elbow than to enter a vein three times the size at the condyle or in the tough loose skin of the radial side of the wrist. The most difficult vein in my experience is the sclerotic vein of the sun-tanned old man, which has lost its fixation through atrophy of the connective tissue. Veins on the back of the hand sometimes

Fig. 262.—Retouching a needle on an oilstone to secure the pointed tip illustrated in Fig. 261. *a'*, *b'*, Viewed from the side. The strokes are made in only one direction—away from the operator.

tempt an operator to his sorrow, although on occasion they are valuable. The more movable the vein and the tougher the skin, the smaller the needle that should be employed. The point of entry on a vein should

be as near the operator and as far from the heart as possible since hemorrhage from a mispuncture may be controlled with a finger, while a second puncture may be made farther up a vein if it is the only one available. The risk of thrombosis is thus diminished by avoiding the passage of an irritating solution over a point of trauma.

Needles.—Close attention should be given to the type and care of needles. In general, I may say that in my experience a series of failures in the hands of a reasonably competent operator is most often attributable to a dull needle, despite the shop maxim that a "poor workman always blames his tools." An improperly sharpened or dull needle jerks, strips the vein, tears holes, or transfixes.

In Figs. 259 and 260 are indicated what seem to me essential points in the needle to be used for intravenous work. The bevel of the majority of needles when first purchased is too long, and by incorrect sharpening they soon tend to become too short.

Fig. 263.—Syringe technic. First motion; entering the skin, showing the tension exerted by the left hand to fix the vein and the pressure with the right for the purpose of steadying the syringe. The needle point is visible under the skin, directly over the vein.

The long, blade-like point of the flat beveled needle is an unknown quantity once it has passed out of sight and is too often embedded in the far side of the vein wall before it seems fairly through the skin. Then follow unexplained leakage and futile efforts to retrieve the lost advantage or to advance the needle farther up the vein. If injection is begun because a good flow of blood has been obtained with a long bevel needle, an infiltration is apt to occur, the mechanism of which is explained by Fig. 261. Flat bevel needles are more easily shut off against the top

of the vein than shorter bevels and confuse the operator into thinking he has failed. The ease with which a long, blade-like point enters the skin makes it very attractive to the novice and often betrays him into difficulties. The defect of the short bevel, which strips the vein without entering it, or tears a hole, is obvious.

The desirable and undesirable type of needle point is illustrated in Fig. 260 and the method of honing a needle on an oil stone to obtain it is shown in Fig. 262. Most needles on resharpening lose the point put on them in manufacturing, and develop at the hands of the average sharpener what is fallaciously supposed to be a cutting edge instead of a point. This inflicts greater trauma on the vein, makes a larger opening for subsequent leakage, and does not "take hold" as well as a needle whose mode of action is to puncture rather than cut.

The gold needle has largely displaced the steel needle in our work, and the care of the needle is greatly simplified by doing away with rusting. Tempered gold needles are cheaper than platinum and retain their

Fig. 264.—Syringe technic. Needle has been advanced, and return flow tested by pulling on piston. A stream of blood should shoot across the fluid if a proper entry has been made. The right hand maintains its pressure.

points reasonably well. They do not leave the brownish tattoo stain in the skin that even a slightly corroded steel needle will leave. For routine syringe technic the 1½-inch gold Luer needle, 20-gage, attaching di-

rectly to the syringe, is satisfactory. The steel hypodermic needle, 22- or 24-gage, is very useful when a very minute and delicate vein at the wrist or on the forehead is to be entered. It should not be resharpened, should be sterilized in phenol and alcohol, should not be used more than three or four times, and should not be more than ½ inch in length, otherwise it may be difficult to secure enough return of blood to demonstrate that the vein has been entered. Through such a needle on a large Luer syringe I have given 50 c.c. of fluid.

For the injection of the larger amounts of fluid by gravity our preference is for the Schreiber needle (Fig. 267) in 17- or 18-gage. Gold needles of that type may be obtained on order, and those in use on my service, while bending rather easily, have given satisfaction.

The advantage of the ordinary filter pump or aspirator for the cleaning of needles with water, alcohol, and ether by suction deserve special mention, when much of this work is being done.

Fig. 265.—Syringe technic. Injection.

The Syringe Technic. —For this technic the needle is attached directly to the syringe, since this does away with the uncertain grip of the fingers on a slippery needle while doing what should be an exact operation. The barrel of a syringe is so much more controllable than a needle that it is now our practice to introduce smaller needles for the gravity method, by a syringe, which is then detached. The needle is always entered bevel up. Four details are essential to the technic. First, the syringe is held flat on the palmar surface of the four fingers of the right

hand, which form a broad bed upon which the syringe is firmly held with the thumb. Second, the movements of the hand and syringe are controlled and the jerk and the unsteadiness can be entirely prevented by firm pressure with the back of the fingers of the syringe-hand on the patient's arm. Third, tension on the skin with the left hand, as shown in Fig. 263 fixes the vein and prevents heaping of the tissues ahead of the needle, with stripping of the vein and a jerky puncture. Fourth, two separate movements, one to enter the skin and one to enter the vein, are essential. The two-movement entry prevents the jerk and over-reaching which is apt to follow the attempt to pierce a soft tissue lying behind a tough one.

The application of these principles is illustrated in Figs. 263, 264, 265 and 266. The needle should be used with the bevel toward the graduations of the syringe so that the dosage can be watched. Entry is made directly over the vein and the first movement carries the slightly inclined needle ¼ inch into the skin over the vein wall, where it is visible
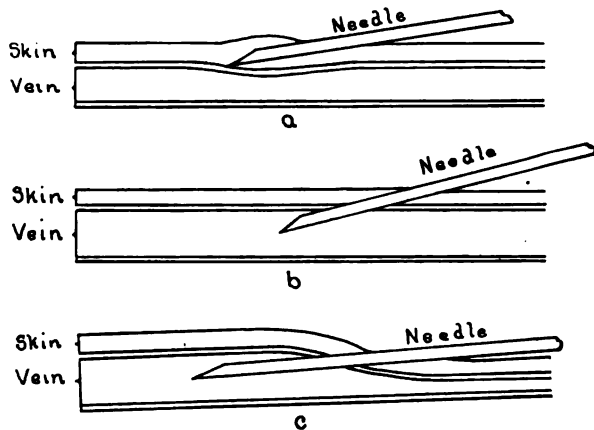
Fig. 266.—Sagittal sections showing the successive positions of the needle in the technic illustrated in Figs. 263, 264, and 265; (a) entering the skin above the vein; (b) angle for entering the vein; (c) advancing the needle after entering.

as an elongated wheal and may be palpated in difficult arms or deep veins. Downward pressure with the whole right hand, syringe, and needle now dimples the top of the vein and a very slightly increased slant carries the needle through the wall with a barely perceptible advance. The pressure of the syringe-hand on the arm is now increased enough to bring the needle practically horizontal and it is then advanced half its length up to the vein and remains stationary. The tension on the skin with the left hand is released as the needle is advanced. The broad base by which the hand controlling the syringe rests on the arm effectively prevents "creeping up" during the injection, with possible puncture of the far side of the vein. The running of the needle above the site of the trauma is, to my mind, instrumental in reducing the likelihood of thrombosis.

With the needle in its final position, the operator pulls back on the piston with the left hand (Fig. 264). If a successful entry has been made, a spurt of blood shoots across the clear fluid in the syringe, and the injection may be begun. If this test is applied *invariably* before the piston is advanced, and repeated once or twice during a difficult injection, the percentage of infiltrates with the syringe technic can be reduced almost to the vanishing point.

The Schreiber Technic.— I have previously called attention to the value of local anesthesia in the introduction of large needles into veins, and further experience has only convinced me the more completely that this detail is essential to the giving of an intravenous injection of original salvarsan *secundum artem.* One minim of a 2 per cent solution of cocain seems to be devoid of danger and acts so quickly that it causes no delay. The introduction of the needle then becomes an exact procedure rather than a haphazard stab. The patient does not disturb the procedure by shrinking away or wincing. His confidence in
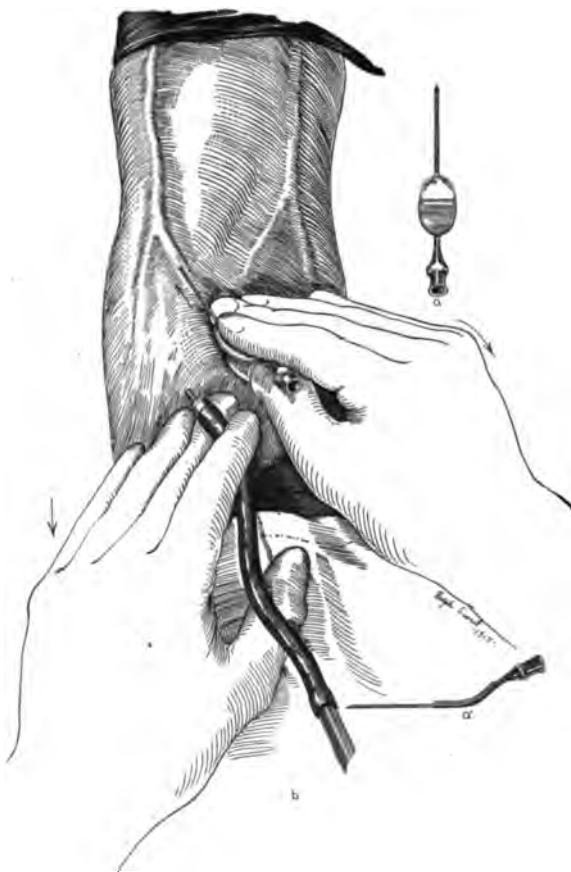
Fig. 267.—*a*, Front view; *a'*, side view, Schreiber needle; *b*, Schreiber needle technic. First motion, needle entering skin. Tension exerted by the last three fingers of both hands. The needle is steadied against the tip of the middle finger, and the entry made by depressing the knuckles rather than by advancing the hand.

the operator is not subject to test. The same principles are used as in the case of the syringe technic. The Schreiber needle is held like a pen (Fig. 267), however, since it is then steadied by two fingers instead of one, and since the position of the hand seems to be more natural after the needle is entered, and must be maintained for a longer time. Pressure on the arm

with the right hand and tension on the skin with the left are again essential. In doing this final step the needle should not be held rigidly. The right hand should relax and the needle be guided by thumb and forefinger rather than forced up the vein. The needle should be run up the vein as in the case of the syringe technic. The movements of the needle in entering suggest those of vertical penmanship, and are accomplished by depressing the knuckles, keeping the wrist fixed, rather than by moving the hand. The needle is introduced detached, and after a free flow of blood is secured the adapter is inserted by the left hand and the injection begun (Fig. 268). The needle should not be released or the right hand moved in difficult veins after the beginning of the injection. There should be a tell-tale in the tube near the needle to show the presence of air, although it is surprising what large amounts may enter a vein without ill effect.

A summary of rules of thumb is appended to be applied seriatim if with either technic a free flow of blood through a needle after introduction or a free flow of fluid into the vein cannot be obtained.

Fig. 268.—Schreiber needle technic. Position of injection. As injection is completed the tubing is compressed just back of the shoulder and the needle withdrawn as a sponge is pressed over the point, without disconnecting.

1. Depress the point of the needle without advancing. The bevel may be shut off against the top of the vein.

2. Palpate the point with the free hand. It is easily recognized if it is still above the vein.

3. In using a syringe, twist the piston in the barrel, pulling backward. It may be stuck.

4. Slowly withdraw the point, if it cannot be felt above the vein, lifting up as you do so. If it has entered the opposite wall it usually comes away with a palpable snap. Then quickly advance again, pressing down hard against the arm with the back of the syringe hand and lifting the point, to flatten the angle of the needle to the vein.

5. If such procedure fail twice, withdraw the needle until the point is just short of the skin puncture, and advance again after repalpating the vein. This is a last resort.

6. If the fifth procedure fails on one or two trials, withdraw the needle entirely and do not reintroduce it until you are satisfied as to its point, and that it is not plugged. Pressure on the vein for five minutes with elevation of the arm while this is being done will often enable you to use the same vein again.

7. Make no comments audible to the patient regarding the condition of your needle.

8. Never try to inject through a hematoma. Use another vein or stop.

9. Never inject and ask if it hurts, if you have the slightest reason to suspect that it will. To inject a little to find whether you are in the vein or not is absolutely inexcusable.

10. Make every effort to have one puncture suffice, using the needle in various directions through the same puncture.

In withdrawing Schreiber needles from veins the aspiration of blood back into the tube by lowering the container, or washing the needle out with salt solution from a separate cylinder, is unnecessary. Pressure made by the nurse over the needle as it is withdrawn, and the shutting off of the stream just back of the adapter and not higher up the tube, will prevent any leakage. After injection the needle can be rinsed by drawing distilled water through it or the elastic recoil of the rubber tube will cause some of the solution to spurt through it when the compressing finger is released. It goes without saying that needles and solution should be fresh when used on clean patients or suspects, and that patients in florid stages should be treated last.

The administration of intravenous medication to small children can be accomplished with ease, as a rule, through the external jugular vein, or through the anterior auricular or the more prominent scalp veins in heredosyphilitic babies. We have thus far found this technic applicable to all cases and have had no occasion to attempt an injection into the superior longitudinal sinus through the anterior fontanel. In all work with small children fine steel hypodermic needles should be used.

OBSERVATIONS ON THE INTENSIVE COMBINED TREATMENTS OF SYPHILIS*

J. H. STOKES

This discussion is based on a preliminary survey, still in progress, of 5500 intravenous injections of salvarsan, neosalvarsan, and arseno-benzol, and the accompanying mercurialization, including 6000 intra-muscular injections of soluble and insoluble mercurial salts, given in the newly organized Department of Dermatology and Syphilology of the Mayo Clinic, during the past fourteen months.

The growing emphasis on intensive antisyphilitic treatment, which has gathered renewed impetus from the discovery of salvarsan and the recognition of the possibilities of abortive cure, has made the term famil-iar. Intensive anti-syphilitic treatment aims at the production of a massive effect on the disease without injury to the patient. In many instances such treatment must be given in a minimum of time, to flood the body, so to speak, in order to meet urgent indications arising from the advance of the morbid process. Treatment must be governed in its intensity by the ease or difficulty with which the particular manifesta-tions are known to yield. It must be further governed by the resistance, the tolerance, and the stamina of the patient. It must be preceded by a skilful estimation of the damage already done, the amount of repair likely to be effected, the prospect for cure or permanent arrest offered by various modes of treatment, and a weighing of the risks of treatment for the patient, as against the risks of the disease. Expert clinical judg-ment in these matters should increasingly rest, not on guess-work and second sight, but on a carefully thought-out and experimentally con-trolled rationale.

In developing the course of intensive treatment given by our service†

† It should be understood that the use of the term "course" in this discussion does not imply a hidebound system of treatment to which all who come are subjected. The necessity of condensing the material of the paper has compelled the writer to express himself in terms of averages, which in the work of the service can be and are departed from as widely in any direction as the exigencies of the special case, considered on its own merits, may require.

I followed a well-known European precedent, less familiar in this country, of combining mercurialization with salvarsanization in the same period of time. The salvarsan dosage was reduced somewhat, and a standard interval adopted (one week) between intravenous injections, employing in addition, according to the indications, one of three agents:

1. Inunctions, one-half to one dram of 50 per cent metallic mercury in cocoa-butter four to six times a week, 40 inunctions to the course.

2. A soluble mercurial salt, mercury succinimide intramuscularly, in $\frac{1}{6}$ grain doses three to five times a week.

3. An insoluble mercurial salt, mercury salicylate, in one-half to two and one-half grain doses once a week, on an ascending scale. Such dosage conforms essentially to what might be called German ideals in the radical treatment of syphilis, and is the basis of such exceptional results as have been reported by Gennerich. The six-weeks' course is necessarily a unit and is repeated at intervals of from one month in early cases to three or more months in late cases.

I regard the intensive course as essentially an emergency measure, with which to abort or suppress an infection in the early primary and secondary stages, to arrest a rapidly advancing or long-neglected process, or to reach parts of the body, or syphilitic conditions which have not yielded, or will not yield, to the older or slower methods. The usefulness of such a course is limited, although in view of the work of Akatsu and Noguchi on spirochætal tolerance of arsenic and mercury, and that of Warthin on the persistence of the spirochæta pallida in the tissues of treated syphilitics, one is often tempted to look on it as universally necessary and desirable. I believe that the usefulness of an intensive course and the efficiency of extraordinary therapeutic methods in syphilis are at present limited, not so much by what they may accomplish for the disease, which is usually a good deal, but by the strain which they put on the patient's physical organization. A successful sterilization may be accomplished and the patient be left with an unknown but serious amount of damage to his kidneys. On the whole, the damage due to an intensive course is not brought about by moderate-dosage salvarsan, but by what are being widely popularized as standard intensive methods for the use of mercury, and particularly by intramuscular injection of the insoluble mercurial salts, such as calomel, the salicylate, etc.

The intensive combined course finds its best application in our hands thus far in the abortive cure of syphilis, in the radical management of secondary syphilis, in early and late syphilis of the nervous system, in

many serious involvements of the eye, as in interstitial keratitis, iritis, etc., in syphilis of the stomach, in destructive gummatous osteoarthritis and osteitis, in mutilating syphilis of the nose, pharynx, and larynx, and in general wherever serious damage is imminent and the patient is still in good condition. The treatment must be tempered with common sense on the part of the physician in latent cases, and benign late manifestations, such as cutaneous syphilids in old people. When damage has been done to important parenchymatous structures, combined salvarsanization and mercurial treatment is less satisfactory, and in marked cardiorenal pathology, and in patients with cirrhotic livers and ascites, it is unsatisfactory and even dangerous.

In our employment of salvarsan, both alone and in combination, we think constantly in terms of the following principles:

1. The drug as such and its impurities seems to be more toxic or at least its toxic effects seem more serious in the vascular mechanism than in any other group of structures.

2. Its effect on the kidney in moderate dosage is negligible. We have given it several times in cases of advanced chronic nephritis, with a phenolsulphonephthalein functional test of 0 to 2.5 per cent, without injury, and even with actual improvement in the condition of patients with syphilis. Acute renal reactions (anuria) are, we believe, primarily glomerular (vascular) injuries, most of which have occurred following too high an initial dose, acid salvarsan, and in pregnancy.

3. The immediate effects of salvarsan on the disease are those of the complex amino-arsenic molecule, or of a "salvarsano-protein." The late complications following its administration are those of arsenic, which is especially stored in the liver, spleen, and skin. Late complications due to cumulative effects and arsenical injuries must be constantly watched for.

4. In the first injection or two salvarsan causes a therapeutic shock —the Herxheimer reaction, which is dangerous in proportion to the importance of the structure most involved by the infection. This has special reference to the meninges and brain, the myocardium, and other vital structures. Even a Herxheimer reaction in a gummatous larynx may asphyxiate the patient unless preparation is made to meet it.

5. Salvarsan is primarily a spirochæticide. It suppresses contagion and clears up lesions, but its effects are transient, and must always be followed up by mercury. Mercury, on the other hand, is an inferior spirochæticide. It will not control contagious lesions but it is a better

builder of immunity. A little salvarsan is worse than none at all, especially in early syphilis, and its indiscriminating or overcautious use leads to premature tertiarism.

6. Old salvarsan we believe should be preferred in early and latent syphilis, wherever there is hope of radical results. We prefer neosalvarsan in visceral syphilis and in children. We utilize the experimentally demonstrated affinity of neosalvarsan for the meninges in the treatment of late syphilis of the nervous system, and avoid it when the process in the nervous system is acute, or likely to be unfavorably influenced by meningeal irritation.

Our daily practice includes an average dosage scale, in a six-injection course, of 0.3, 0.4, 0.4, 0.5, 0.6, 0.5 old salvarsan. Six injections with a weekly interval represents, in our experience, average tolerance. If extended beyond this number, the intervals between injections must be lengthened. We do not exceed 3 decigrams of old salvarsan or neosalvarsan as an initial dose, except for provocative effects. A 1-decigram initial dose for cardiac cases is not exceeded. The dosage is reduced in late syphilis, or in cases in which only palliative results are expected, especially in patients with damaged livers and spleens whose storage capacity and tolerance is low. We never give more than half a decigram as an initial dose to children under 60 pounds in weight. In abortive treatment, repeated maximum doses of 6 decigrams are given after the 3-decigram initial dose.

We believe it a conservative rule never to give a single injection of salvarsan except for provocative effect; seldom less than three are given in a late case without contraindications and never less than six in an early case (primary or secondary).

An empty stomach and restricted diet prevent reactions. A cathartic twenty-four hours after injection prevents toxic absorption of the part of the salvarsan eliminated by the bowel. In case of threatened reactions the patient must be alkalinized with sodium bicarbonate or Fischer's solution by bowel. The solution of old salvarsan should be slightly alkalinized.

Salvarsan should not be given without mercurial preparation in acute processes other than syphilitic nephritis or syphilis in the abortive stage. We never give salvarsan in ambulatory cases, and believe such a method is especially dangerous in cardiovascular, severe visceral, or acute central nervous system syphilis. The interval should be tripled and the dose halved after a toxic erythema if the injection is to be re-

peated, or an exfoliative dermatitis may result. Irritating applications, including mercurial inunctions, should not be used on the skin after a toxic erythema. In acute reactions occurring on the table, and later in incipient cerebral accidents, adrenalin should be used subcutaneously (5 to 10 mm. average dose). Well-compensated hypertension does not contraindicate salvarsan in moderate doses. Salvarsan should not be given to confirmed alcoholics. An injection of salvarsan in a patient who shows well-defined mental symptoms after injection should not be repeated, but a prolonged mercurial course should be substituted. Basing our opinion on 1400 injections, we have concluded that arsenobenzol (Dermatological Research Laboratories) is fully the equal in therapeutic efficiency of the German old salvarsan and very much superior to it on the score of lower toxicity.

The preliminary survey of the year's results in intensive mercurial treatment has convinced us that, while salvarsan may give rise to abrupt and immediate complications, mercury is the insidiously dangerous factor in the treatment of syphilis, especially when used according to modern radical standards. Prolonged mercurialization by intramuscular injection inflicts at first temporary, but later cumulative, damage on the kidney, and may give rise to a severe and obstinate nephritis, even though the gastro-intestinal tract and the mouth show no reaction whatever and the patient makes rapid symptomatic improvement so far as his syphilis is concerned. Our studies seem to support the following tentative conclusions:

1. Mercurial inunctions may give rise to marked renal irritation in spite of a reputation to the contrary. They are, however, much less apt to do so than soluble or insoluble mercurial salts, intramuscularly. The soluble mercurial salt (succinimid) has a distinctly higher therapeutic efficiency than the insoluble, but possibly less effect on the Wassermann reaction in early cases. It is the salt par excellence for the therapeutic test and for the treatment of central nervous system syphilis. It exhibits cumulative effects to some extent and irritation may appear at the end of a first course or be postponed until a later course, even though the second be preceded by a rest period. About 50 per cent of our patients who received the soluble salt showed some evidence of its effect on the kidney.

Insoluble injections are dangerously cumulative. The storage of the drug in the tissues (50 per cent in six weeks, according to Shamberg) reduces subsequent therapy to guesswork and at any time serious com-

plications may appear without warning. A single such course may leave so much mercury deposited in the tissues in a problematic state of absorbability that even a mild interim course of inunctions will give rise to a marked nephritis. In our experience, the insoluble salt is more apt to provoke renal irritation than is the soluble. Nearly 70 per cent of our patients receiving insoluble injections showed renal disturbances at some time during the treatment

The maximum total dosage of mercury salicylate tolerated without renal reaction by the cases thus far included in our survey was thirteen and one-half grains, which is less than the total in the ordinary 1½-grain, 10-injection course.

Absorption of intramuscularly injected mercury is fully as dependent, we believe, upon accidents of absorption as upon dosage. Encapsulation, gradually increasing fibrosis in the tissues of the buttock, a wide area of distribution over the fascia lata above the gluteus maximus, trauma to the injection site, etc., distinctly influence the absorption of the drug and its effect on the kidney.

Different individuals show wide variation in their tolerance of mercury, and we have as yet been unable definitely to predict the degree of individual tolerance before beginning treatment. Age thus far seems to be a factor of minor importance. Fluctuations in individual tolerance during a single course are apparent, influenced possibly by accidents of absorption, dietary errors, etc. Due allowance should be made for spontaneous variations in urinary findings.

The presence of casts in the urine is the most reliable single criterion on which to judge the reaction of the kidney to mercury. The mouth and gastro-intestinal tract should not, therefore, be used by practitioners as evidence of tolerance of the drug, since renal damage may be manifest long before the appearance of stomatitis or diarrhea. Any examination of the urine made without a microscopic study of the sediment is worthless. Albumin fluctuates erratically, specific gravity is inconstant in its variations, and only once, even under high dosage, have we seen hematuria which we believed to be traceable to the effect of mercury.

Stomatitis and gastro-intestinal accidents as factors in mercurialization can be practically eliminated by sufficiently rigorous prophylaxis. Avoidance of acid foods, the use of alkaline, astringent, and oxidizing mouth prophylaxis, and the elimination of fruits and coarse vegetables

from the diet are the main essentials.   Strict regard for these principles has practically done away with such complications on our service.

Those employing intensive methods should be familiar with the over-treatment syndrome which appears occasionally.   It seems to include hyperirritability, extreme nervousness, insomnia, and emotional instability possibly due to excessive salvarsan, marked loss of weight, weakness, a pinched and withered facial expression with pallor, and indefinite aches and pains with stiffness of the joints.   The latter features we interpret as part of the toxic effect of mercury, and we have noticed that they may occur in persons receiving mercury, alone whose kidneys, mouths, and gastro-intestinal tracts show no evidence of the intoxication.

Dealing with resistant late cases, our combined course of treatment is apparently successful in reversing the Wassermann test in approximately 60 per cent.   Our symptomatic results seem exceptionally good at least thus far in bringing about the arrest of gastric crises, and the control of ataxia, sensory disturbances, and the lightning pains of tabes dorsalis.   We have been able to cause the apparent involution of early Charcot joints.   Gastric syphilis as such, interstitial keratitis, even of long standing, and vascular lues of the meninges and brain show striking improvement in a single course.   Osseous and cutaneous lues, early and late, offer no special difficulties.   The results are less satisfactory in spastic and parenchymatous degenerative central nervous system changes and in visceral involvement, where the damage done is, of course, irreparable.

Two neuro-recidives and one death have been seen in 5500 injections of salvarsan—the death, the result of a typical hemorrhagic encephalitis which developed following an alcoholic debauch in a patient in whom every precaution had been used in the regulation of dosage and intervals.   The symptoms appeared three days after an injection of German neosalvarsan.   Our first neuro-recidive occurred in a patient who, because of pernicious anemia, had received salvarsan only.   It followed the seventh injection while the patient was Wassermann negative and involved the seventh and eighth nerves.   The second developed in an infection of a year's duration, in the middle of a course of mercury salicylate injections.

Summarizing, we have come to regard the effect of mercury on the kidney as the weak point in radical methods in the management of syphilis.   This applies with special force to the intramuscular injection,

and especially to the injection of insoluble mercurial salt, the convenience of which may easily be counterbalanced by much damage that goes undetected because of the irksomeness, to the majority of physicians, of the frequent careful urinalysis. *We believe radical treatment to be indispensable* and therefore urge the devising of means to protect the kidney especially from its very real dangers.

We have formulated the five most important deductions to be drawn from the year's work of the Section as follows:

1. Have a wholesome respect for the vascular toxicity of salvarsan and the renal toxicity of mercury.

2. Use radical methods discriminatingly, when radical results may be secured.

3. Examine the urine repeatedly microscopically.

4. Watch for cumulative effects everywhere.

5. To discontinue the use of the insoluble mercurial salts.

HEAD, TRUNK, AND EXTREMITIES

THE PRODUCTION OF AN ANTIPOLIOMYELITIS SERUM IN HORSES

BY INOCULATIONS OF THE PLEOMORPHIC STREPTOCOC-CUS FROM POLIOMYELITIS *

E. C. ROSENOW

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It is a well-established fact that the serum of patients and monkeys which have recovered from poliomyelitis has a neutralizing[1] and protective power[2] against the virus of poliomyelitis. Inoculations of virus as well as of cultures of the globoid organism[3] which fail to produce at least abortive attacks of poliomyelitis fail also to produce neutralizing and protective substances in the serum; hence immunity does not result. The recent work of Amoss[4] proves further that the globoid organisms of Flexner and Noguchi[5] have indeed little antigenic power. The need of immunization experiments along other lines in this disease is therefore apparent.

A restudy of the bacteriology of poliomyelitis during the past epidemic has emphasized anew the possible rôle which bacteria of ordinary size may play in the etiology of this disease. A pleomorphic streptococcus or micrococcus having elective affinity for the central nervous system in animals has been isolated quite constantly from the atrium of infection and the central nervous system,[6] the brain and cord,[7] and the spinal fluid[8] in human poliomyelitis, and from the central nervous system of monkeys paralyzed with virus.[9]

It has been shown that under certain anaërobic conditions the organism may become exceedingly small, filtrable, and anaërobic, resembling very closely the globoid organisms of Flexner and Noguchi. Moreover, the mechanism by which the large forms become small has been demonstrated.[9] Injections of the large form of this organism into two

monkeys soon after isolation has rendered the animals immune to virus,[10] a result not obtained with a streptococcus from another source.*

On the basis of these results, immunization experiments with aërobic cultures of the pleomorphic organism were instituted.

Recently Nuzum has reported on the protection of animals against the large form of the organism with the serum from a horse that had been injected repeatedly with aërobic cultures. Mathers and Tunnicliff[11] have shown a specific increased opsonic power of the serum toward this organism in poliomyelitis in children. Neustaedter and Banzhaf[12] appear to have developed a neutralizing serum in a horse by injecting large doses of filtrates of active virus.

I wish now to record the essential facts in the immunization of horses with cultures of the pleomorphic streptococcus, the results of experiments in neutralizing and protecting against virus with the immune serums thus obtained, and the findings of agglutination and complement-deviation studies.

IMMUNIZATION OF HORSES

The method followed for immunizing horses was that worked out by Flexner and Amoss[13] and Amoss and Wollstein[14] in the production of antidysentery and antimeningitis serum, respectively. Advantage was thus taken of the principle first noted by Fornet and Müller,[15] Bonhoff and Tsuzuki,[16] and Gay and his pupils,[17] of the very rapid production of antibodies following injections of antigen at brief intervals.

Increasing quantities of the pleomorphic streptococcus were injected intravenously for three consecutive days, this being followed by a rest period of seven days. A desensitizing dose of approximately one-tenth of the immunizing dose was given on the first day of each period after the first. The immunizing dose of the first day of each period was that of the last previous injection. The dose on the second and third days of each series was increased approximately by one-tenth. The temperature was used as a guide to dosage. If the temperature which rose soon after the injection had not returned to normal at the time for the next injection, the antigen was not given until it had returned to normal.

The bacteria for injection were grown aërobically in ascites-dextrose broth or dextrose broth in tall columns for from eighteen to twenty-four hours at from 33 to 35 C. (91.4 to 95 F.). After centrifugaliza-

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* At the time these experiments were reported, the monkeys had resisted one intracerebral injection of highly active virus. Since then they have resisted three or four injections, each of highly active virus, without showing symptoms of poliomyelitis.

tion, the supernatant broth was decanted and the bacteria were either washed or directly suspended in salt solution so that 1 c.c. of the suspension contained the growth from 15 c.c. of the broth culture.   Most of the suspensions used were freshly prepared, but in some instances they had been kept in the ice-chest for several weeks.   All strains injected were cultivated for at least two generations, nearly all having been plated at least once on blood-agar.   Blood-agar cultures were made of all suspensions at the time of injection.

Various methods have been employed for maintaining the original immunizing properties.   Strains have been cultivated under anaërobic and aërobic conditions on blood-agar slants, in deep stabs of ascitic tissue agar and in tall tubes of ascitic tissue fluid.   Strains from human poliomyelitis have been kept in latent life by preserving the brain and cord substance from animals paralyzed with cultures, in sealed pipets in the ice-chest.   Portions of the brain and cord and large quantities of recently isolated cultures from human and monkey poliomyelitis have been dried in vacuo.

EXPERIMENTS

HORSE 1.—A large black horse, four years old, weighing approximately 1600 pounds, was given injections which were begun November 2, 1916, and were continued until May 1, 1917.   The first three injections contained heat-killed (60 C.—140 F., thirty minutes) strains from the brain and cord of human poliomyelitis, the next nine injections contained strains both from human poliomyelitis and paralyzed monkeys, and all subsequent injections contained cultures of the pleomorphic streptococcus isolated from the brain and cord of monkeys paralyzed with virus in the usual way.   The doses ranged from the equivalent of the growth from 160 c.c. of broth to as high as the equivalent of the growth from 1400 c.c.   Test bleedings were made previous to the first injection, and November 2, November 4, December 22, January 8, January 30, March 3, April 3, May 14, and May 16.   December 27, three days after the third injection of living bacteria, the horse had fever, and his hind extremities were so weak that he could scarcely get up.   The fever and weakness soon disappeared.   April 5, a suspension containing staphylococci was injected accidentally.   April 7, the horse had fever and developed arthritis of the right hock.   April 9, he had arthritis of the knee of the left foreleg.   April 17, the fever had disappeared, the arthritis had largely subsided, and the injections were resumed.   Dead cultures, however, were now injected for the next three series of injections.   The last dose was given May 1, and consisted of the growth from 600 c.c. of broth of a strain in the third generation from a recently paralyzed monkey.   May 14, the animal was unable to get up on account of weakness

in the hind extremities. It was bled 6000 c.c. May 16, weakness of the hind extremities still prevented it from getting up. It was then etherized and bled to death, approximately 36,000 c.c. of blood being obtained. A moderate amount of serous fluid was found in the left ankle-joint and the right hock. There were no lesions of the viscera except a few subendocardial hemorrhages in the right ventricle. The vessels in the gray matter of the lumbar cord were hyperemic. Cultures of the blood yielded a staphylococcus, and those from the spinal cord showed diphtheroid bacilli. Frozen sections of the lumbar cord revealed little or no round-cell infiltration.

HORSE 2.—A large bay, eight years old, weighing approximately 1200 pounds, was injected at intervals, according to the method described, with live cultures from human and monkey poliomyelitis in relatively massive doses from November 22 to December 13. During the eighth injection (December 13) he developed marked symptoms of acute anaphylactic shock and died in a few minutes. He was bled just previous to injection and soon after death.

HORSE 3.—A medium-sized bay, three years old, weighing approximately 1200 pounds, has been injected according to schedule since January 30, 1917. The pleomorphic streptococcus from human poliomyelitis has been employed exclusively. The first six injections consisted of suspensions of the dried bacteria prepared last summer from strains recently isolated from the brain and cord. Later, there were added suspensions of strains found to be agglutinated in high dilution by the serum of Horse 1 and grown continuously on blood-agar, in deep stabs of ascitic tissue agar, or filed away last summer in sealed pipets containing the aspirated brain substances of rabbits and guinea-pigs paralyzed with cultures. Except for alarmingly severe symptoms on several occasions immediately following the injections, this horse has remained well. Test bleedings were made January 30 (before injection), March 2, April 3, and May 14.

THE EFFECT OF IMMUNE HORSE SERUM ON VIRUS IN VITRO

In these experiments the technic followed was that used by other workers in this field. Five per cent emulsions of physiologic sodium chlorid solution of fresh or glycerinated brain and cord were prepared by grinding the material in a mortar with sterile quartz sand, filtering it repeatedly through paper or in some instances passing it through a Berkefeld filter. The filtrate was thoroughly mixed with the serum to be tested, and, for controls, with the sodium chlorid solution and the corresponding normal serum. It was then placed in the thermostat for two hours and in the ice-chest for from eighteen to twenty-two hours. All monkeys (*Macacus rhesus*) were injected intracerebrally, under ether,

with 1 c.c. of the respective mixtures.   In each series of experiments the monkeys chosen were of approximately the same weight.

TABLE 1.—THE EFFECT OF VARIOUS IMMUNE SERUMS ON VIRUS

MONKEY	INOCULATION	RESULT
103	Virus + NaCl solution; control	Mild symptoms; resisted second inoculation
93	Virus + normal monkey serum; control	Mild symptoms; resisted second inoculation
102	Virus + normal horse serum; control	Severe symptoms; etherized, thirteenth day
94	Virus + virus immune serum; Monkey 24	Remained well
95	Virus + culture immune serum; Monkey 43	Severe symptoms; recovered
96	Virus + culture immune serum; Monkeys 53 and 61	Remained well
97	Virus + culture immune serum; Rabbit 1078	Severe symptoms; etherized
98	Virus + acquired immune serum; Human 802	Remained well
99	Virus + acquired immune serum; Human 784	Remained well
100	Virus + culture immune serum; Horse 1	Remained well
101	Virus + culture immune serum; Horse 1; 1 : 1000	Remained well; paralyzed by second inoculation

The experiment summarized in Table I was begun February 7, 1917. The emulsion was prepared from fresh brain and cord of Monkey 85, which became paralyzed on the eighth day following the injection of a virus which had been passed successively through six monkeys.   The first three experiments (Monkeys 103, 93, and 102) served as controls. All developed mild but unmistakable symptoms of poliomyelitis.   Monkey 94, injected with virus digested with serum from Monkey 24, which had recovered from poliomyelitis, served as an additional control in that it showed the technic to be adequate for the destruction of virus by serum known to have such action.   Monkey 95 developed severe paralysis, the serum of Monkey 43 not having destroyed the activity of the virus.   Monkey 43 had been injected previously with a strain of streptococcus grown large from typical globoids, and was found later not to be immune to virus.   Monkeys 53 and 61, whose serums destroyed virus, as evidenced in the experiment on Monkey 96, had been immunized with cultures of the pleomorphic streptococcus recently isolated from paralyzed monkeys.   Their serums agglutinated specifically the pleomorphic streptococcus from both human and monkey poliomyelitis.

The serum of Rabbit 1078, which was used in the experiment on Monkey 97, had no digestive action on virus. Rabbit 1078 had been injected repeatedly with the heat-killed pleomorphic streptococcus. When used, its serum had been kept in the ice-chest for forty days. The serums used in the next two experiments (Monkeys 98 and 99) were obtained from cases of sporadic anterior poliomyelitis, and destroyed the activity of the virus. The serum used to digest the virus in the last two experiments (Monkeys 100 and 101) was obtained from Horse 1, January 30, 1917, eight days previously. It destroyed the activity of the virus completely, even in a dilution of 1 : 1000.

TABLE 2.—EFFECT OF IMMUNE HORSE SERUM ON VIRUS

MONKEY	INOCULATION	RESULT
112	Virus + NaCl solution; control	Mild symptoms; recovered; resisted second inoculation
113	Virus + normal horse serum; control	Mild symptoms; recovered; died from ulcerative colitis, thirty-fifth day
114	Virus + immune serum; Horse 1	No symptoms; died of ulcerative colitis, twenty-first day; no infiltration
115	Virus + immune serum; Horse 1; 1 : 1000	No symptoms; paralyzed by second inoculation
116	Virus + serum from sporadic poliomyelitis (521)	No symptoms; paralyzed by second inoculation

In the experiment summarized in Table 2, the same virus after passage through one more monkey (Monkey 106) was used while fresh. The experiment was again controlled both positively and negatively. The controls with sodium chlorid solution and normal horse serum developed poliomyelitis, but the control with human poliomyelitis serum did not. The horse serum used was obtained the day previously (March 2, 1917) from Horse 1. As in the previous experiment, it destroyed activity of the virus in dilutions of both 1 : 1 and 1 : 1000.

The experiment summarized in Table 3 was begun April 15, 1917. The effect of the serum from both Horse 1 and Horse 3 was tested against highly active glycerinated virus that had been passed through a Berkefeld filter. The control (Monkey 141) became completely paralyzed in six days, and was etherized when respiratory failure was imminent. The activity of the virus appeared to be diminished but not wholly destroyed by an activated mixture of serums from Horse 3, as shown by the experiment on Monkey 143. In dilutions of 1 : 1000 the serum

had little or no effect (Monkey 144). In the experiment on Monkey 146, an activated mixture of the serum from Horse 1 (January 30, March 3, and April 3) appeared to diminish the activity of the virus, as manifested by a delay of eight days over the control for the onset of paralysis, by the comparative mildness of the paralysis, and by the fact that the monkey recovered. In dilutions of 1 : 1000 this mixture of serums had no effect (Monkey 145).

TABLE 3.—THE EFFECT OF IMMUNE HORSE SERUM ON FILTERED VIRUS

MONKEY	INOCULATION	RESULT
141	Virus + NaCl solution; control	Symptoms, fifth day; completely paralyzed, sixth day; etherized
143	Virus + immune serum; Horse 3	Symptoms, eighth day; severely paralyzed, tenth day; recovered
144	Virus + immune serum; Horse 3; 1 : 1000	Symptoms, sixth day; completely paralyzed, seventh day; etherized
146	Virus + immune serum; Horse 1	Symptoms, thirteenth day; severely paralyzed, sixteenth day; recovered
145	Virus + immune serum; Horse 1; 1 : 1000	Symptoms, fifth day; completely paralyzed, sixth day; died, seventh day

In an experiment performed February 20, 1917, the inactivated serum from Horse 1, which was obtained January 30 and which digested virus when fresh (Table 1), had only a slight destroying power over highly active fresh virus, the onset of the paralysis in two monkeys being delayed only one and two days, respectively, over that of the control. April 23, the serums of the bleedings of Horse 1 from January 30 to April 3 were mixed, and on April 24 the mixture was passed through a Berkefeld filter. This filtered mixture in one experiment was found not to diminish the activity of the virus. It appeared, then, that when fresh, the serum obtained January 30 and March 2 from Horse 1, immunized chiefly with the pleomorphic streptococcus from monkeys paralyzed with virus, had the power to destroy the activity of fresh, moderately virulent virus completely and to inhibit the effect of highly virulent glycerinated and filtered virus, a power which it appeared to lose on standing. The serum from Horse 3, immunized entirely with strains from human poliomyelitis isolated a long time previously, had no apparent effect.

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PROTECTION OF MONKEYS AGAINST EXPERIMENTAL POLIOMYELITIS
WITH IMMUNE HORSE SERUM

In Table 4 are summarized 3 series of experiments which were under-
taken to determine the protective power of immune horse serum against
intracerebral injections of virulent virus. The serum from Horse 1 used
in the first series of experiments, begun February 7, was obtained Janu-
ary 30.

TABLE 4.—PROTECTION OF MONKEYS AGAINST POLIOMYELITIS WITH
IMMUNE HORSE SERUM

MONKEY	INOCULATION	TREATMENT	RESULT
89 2.3 kg.	0.5 c.c. Virus 85	Intraspinal and intravenous injections of immune se-rum; Horse 1	No symptoms for fifty-six days; slight symptoms fol-lowing second inoculation
90 3.8 kg.	1 c.c. Virus 85	Intraspinal and intravenous injections of immune se-rum; Horse 1	No symptoms for fifty-six days; severe paralysis, ninth day after second in-oculation
91 2.2. kg.	0.5 c.c. Virus 85	Alternate subcutaneous and intravenous injections of heat-killed pleomorphic streptococcus	Severe paralysis, eleventh day; no improvement fol-lowing injection of immune serum, Horse 1; died of colitis, nineteenth day
92 2.5 kg.	0.5 c.c. Virus 85	Subcutaneous injections of heat-killed pleomorphic streptococcus	Severe paralysis, thirteenth day; recovered following in-jections of immune serum, Horse 1
147 3.5 kg.	0.5 c.c. Virus 889	None; control	Symptoms, fifth day; severe paralysis, seventh day; prostrate, tenth day; ether-ized
149 3.6 kg.	0.5 c.c. Virus 889	One intravenous injection of sensitized pleomorphic streptococcus, eleven days previously	Symptoms, twelfth day; se-vere paralysis, thirteenth day; recovered
173 1.8 kg.	0.5 c.c. Virus 165	None; control	Severe paralysis, seventh day; apparent protection follow-ing injection of immune serum, Horse 1; recovered
174 1.8 kg.	0.5 c.c. Virus 165	Intravenous injections of im-mune serum; Horse 3	Severe paralysis, tenth day; recovered
175 1.7 kg.	0.5 c.c. Virus 165	Intravenous injections of im-mune serum; Horse 1	No symptoms; well twenty-fourth day

Simultaneous intraspinal injections of 2 c.c. and intravenous injec-
tions of from 5 to 10 c.c. were made for two consecutive days. Five
additional intravenous injections of from 5 to 14 c.c. were made every
second or third day. The animals were completely protected, as shown
by the controls (Monkeys 91 and 92) which were injected with a vaccine.
They succumbed to poliomyelitis, however, following a second injection
two months later, a further proof that infection had not occurred. Ad-

ditional evidence of the activity of the virus is afforded by the results recorded in Table 1, this series of monkeys having been inoculated with the same virus.

In the experiments on Monkeys 147 and 149 (outlined in Table 4), the effect of a single immunizing dose of the sensitized pleomorphic streptococcus was tested against a heterogeneous virus of high virulence.*

A mixture of strains from human poliomyelitis isolated last summer and recently isolated strains from paralyzed monkeys were grown in dextrose broth, washed in sodium chlorid solution, and suspended in the filtered mixture of the serum from Horse 1. The bacteria were agglutinated almost immediately, and after the suspension had been kept at 35 C. (95 F.) for two hours, were washed in sodium chlorid solution. Five c.c. of a rather dense suspension were then injected intravenously. That a degree of protection was afforded was indicated by a delay of seven days in the onset of the paralysis over that of the control, by the comparative mildness of the symptoms, and by recovery of the animal.

In the last series of experiments, summarized in Table 4, the serums were obtained on the day the experiments were begun, May 14. Intravenous injections of 10 c.c. were made immediately after inoculation of virus, the following day, and then every second day for four additional injections. The serum from Horse 3 had slight protective power, there being a delay of only three days over the control in the onset of symptoms (Monkey 174). The serum from Horse 1, on the other hand, completely protected Monkey 175, and two intravenous injections of 12 c.c. each appeared to protect the control (Monkey 173) from a fatal attack.

The effect of the curative properties of these serums after paralysis had begun has been tested, in all, in 24 monkeys. Simultaneous intraspinal (2 c.c.) and intravenous (from 5 to 12 c.c.) injections were given in 3 instances, and intravenous injections (from 10 to 12 c.c.) in the others. In no instance were injections made oftener than once in twenty-four hours. If the serum had been kept for some-time in the refrigerator, it was usually activated with guinea-pig complement, just previous to injection.

If the serum appeared either to lessen the symptoms or to arrest the paralysis, or if the treated animals recovered when the untreated controls died of respiratory failure or surely would have died if they had not been etherized, the result was put down as favorable. If it had no apparent effect, it was put down as indifferent.

* Kindly sent me by Dr. W. E. Wayson, of the Public Health Service, Washington, D. C.

Out of 7 treated monkeys in which the results were indifferent, four showed severe ulcerative colitis, two marked tuberculosis, and one meningitis due to hemolytic streptococcus. These, therefore, were not suited for testing the efficacy of the serum. Of the remaining 17, the serum from Horse 3 was injected into 4 (once in one, twice in two and three times in one), with no apparent effect on the course of the disease in any instance. Three of these monkeys died, and one was etherized when respiratory failure seemed imminent. The remaining 13 were treated with the fresh or activated serum from Horse 1. The results were indifferent in 3 and favorable in 10. All of the former received only 1 injection. Of the latter, 2 received 1 injection; 2, 2 injections; 1,
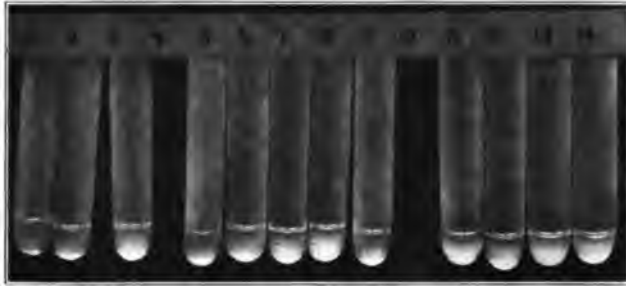
Fig. 269.—Agglutination of pleomorphic streptococcus from human poliomyelitis. This strain was not used in the immunization of horses. Tubes 1 to 3 contain normal horse serum; Tubes 5 to 9, immune serum from Horse 1; Tubes 11 to 14, immune serum from Horse 3. The dilutions of serum and antigen (dextrose broth culture) are 1:1, 1:10, 1:100, etc., respectively, in each series. Note agglutination in low dilutions and its absence in higher dilutions by the normal horse serum, and the absence of agglutination in low dilutions and marked agglutination in high dilutions by the immune serums.

3 injections; 1, 4 injections; 3, 5 injections, and 1, 7 injections. All of the 10 recovered, with varying degrees of residual paralysis.

The experiments on the protective and curative power of these immune serums, therefore, indicate that while the serum from Horse 3 had little or no effect, the serum from Horse 1 had definite protective and curative power, a finding directly in accord with the results of the neutralization experiments.

PROTOCOLS OF EXPERIMENTS

Protocols of the last three experiments summarized in Table 4 will serve to illustrate:

EXPERIMENT 1.—*Control.*—Monkey 173. *Macacus rhesus.* 1.8 kg.
May 14, 1917: Etherized; 0.5 c.c. of glycerinated virus (751^{10}) from Monkey 165 injected into right frontal lobe.

May 15–18: Appeared well.

May 19: Appeared irritable, no weakness.

May 20: Irritable and undoubtedly weak in left leg.

May 21, 8.30 A. M.: Tremor of head and muscles of hind extremities; unable to bear weight on legs, and dragged the right.   *4 P. M.:* Undoubtedly weaker; dragged both legs; had tremor and weakness of muscles of left arm.   Twelve c.c. of immune serum from Horse 1 (obtained May 14) injected intravenously.

May 22, 8 A. M.: Definitely weaker in hind extremities; no extension of paralysis in arms.   *3 P. M.:* Injection of serum repeated.

May 23: Only slightly weaker in hind extremities; no demonstrable weakness in arms.

May 24: Right arm badly paralyzed; hind extremities completely flaccid; left arm also weak, but monkey could move it in all directions.

June 2: Marked improvement; the tremor of the head had disappeared; arms stronger, animal pulled himself on perch; able to sit up but legs still flaccid.

June 7: Improved.

EXPERIMENT 2.—*Attempt to protect against virus with serum from Horse 3.*   Monkey 174, *Macacus rhesus*, 1.9 kg.

May 14, 1917, 5 P. M.: Etherized; 0.5 c.c. glycerinated virus (751[10]) from Monkey 165 injected into right frontal lobe.   *5.10 P. M.:* Twelve c.c. immune serum, Horse 3 (obtained May 14), injected intravenously.

May 15, 12 M.: Appeared well; injection of serum repeated.

May 17, 9.30 A. M.: Appeared well; injection of serum repeated.

May 19, 3.30 P. M.: Appeared well; injection of serum repeated.

May 20: Appeared well; no weakness.

May 21, 7.30 A. M.: Appeared slightly irritable, but no weakness. *4 P. M.:* Injection of serum repeated.

May 22, 3 P. M.: Extremely irritable; fur roughened; weakness of hind extremities; injection of serum repeated.

May 23: Weaker, very tremulous.

May 26: Marked paralysis of all extremities; some power in left arm; tremor of head still present.

June 2: Severe paralysis of all extremities; can move left arm slightly; tremor of head still present but less marked.

June 7: Condition much the same as on June 2.

EXPERIMENT 3.—*Attempt to protect against virus with serum from Horse 1.*   Monkey 175, *Macacus rhesus*, 1.8 kg.

May 14, 1917, 5.20 P. M.: Etherized; 0.5 c.c. of glycerinated virus (751[10]) from Monkey 165 injected into right frontal lobe.   *5.30 P. M.:* Twelve c.c. of immune serum from Horse 1 (obtained May 14) injected intravenously.

May 15, 12 M.: Appeared well; injection of serum repeated.

May 17: Appeared well; injection of serum repeated.

May 19: Appeared well; injection of serum repeated.

May 20: Appeared well; no weakness.

May 21, 7.30 A. M.: Appeared well; no weakness. *4 P. M.:* Injection of serum repeated.

May 22, 3 P. M.: Appeared well; injection of serum repeated.

May 23: Appeared well; no weakness.

June 7: Has appeared well and has shown no symptoms of poliomyelitis at any time.

AGGLUTINATION AND COMPLEMENT-DEVIATION EXPERIMENTS

Numerous agglutination experiments have been made with the pleomorphic streptococcus, with the serums from immunized horses, with the serums from patients who have recovered from poliomyelitis, and with the serums of monkeys paralyzed with virus. As controls, normal serums of these species and numerous strains of streptococci from sources other than poliomyelitis have been used.

The agglutinating titer of the serums of the horses (especially Horse 1) has become very high, agglutinations having been obtained in dilutions as high as 1 : 1,000,000. The serums from both Horse 1 and Horse 3 agglutinated alike the strains from human and monkey poliomyelitis, as shown in the illustration, Figure 269. By the use of these serums it is now possible to differentiate the strains which appear to bear etiologic relation to poliomyelitis from strains of streptococci found in tonsils which undoubtedly have no such relation, and from strains of streptococci which may be found occasionally in the nervous system of uninoculated animals.

The serums from 23 patients who had recovered from poliomyelitis, and the serums from 27 monkeys which became paralyzed following injections of virus, have been found to agglutinate specifically the pleomorphic streptococcus isolated both from poliomyelitis in man and from experimental poliomyelitis in monkeys. The serums from 43 persons who have not had poliomyelitis, and the serums from 27 normal monkeys, failed entirely to agglutinate these strains, or agglutinated them in lower dilutions than the respective immune serums. Only two of a large number of strains of streptococci from a wide range of sources were agglutinated by poliomyelitic serums to a degree comparable to the agglutination of the pleomorphic streptococcus. Antipneumococcus, antistreptococcus, antimeningococcus, and antigonococcus serums had little or no more agglutinating power over these strains than normal horse serum.

Complement-deviation tests made by Dr. Sanford, while incomplete, show that both Horse 1 and Horse 3 have developed specific antibodies that in high titer have complement-deviating properties with the antigens made from strains isolated from human poliomyelitis and from experimental poliomyelitis in monkeys. Moreover, by using these immune horse serums for determining the properties of bacterial suspensions from various sources, it has been found in many instances that strains isolated from both human and monkey poliomyelitis have marked antigenic properties, while similarly prepared antigens from other sources do not have these properties.

SUMMARY

It has thus been shown that:

1. The serum of horses immunized with aërobic cultures of the pleomorphic streptococcus from both poliomyelitis in man and experimental poliomyelitis in the monkey developed specific antibodies, agglutinins, and complement-deviating properties, the agglutinins appearing to be present in large amount because the serums cross-agglutinate these strains specifically in very high dilutions.

2. The serum of patients and monkeys which have recovered from attacks of poliomyelitis cross-agglutinates specifically many, but not all, of these strains in the lower dilutions.

3. What is of greatest significance, the serum of the horse immunized with recently isolated strains from experimental poliomyelitis in the monkey appears to have developed neutralizing, protective and curative power against the virus of poliomyelitis.

REFERENCES

1. Levaditi, C., and Landsteiner: Recherches sur la paralysie infantile experimentale, Compt. rend. Acad. d. sc., 1910, cl, 131.
2. Flexner, S., and Lewis, P. A.: Epidemic poliomyelitis in monkeys: The activity of the virus, Jour. Am. Med. Assn., 1910, liv, 45–46.
3. Flexner, S.; Noguchi, H., and Amoss, H. L.: Concerning survival and virulence of the micro-organism cultivated from poliomyelitic tissues, Jour. Exper. Med., 1915, xxi, 91–102.
4. Amoss, H. L.: The cultivation and immunological reactions of the globoid bodies in poliomyelitis, Jour. Exper. Med., 1917, xxv, 545–556.
5. Flexner, S., and Noguchi, H.: Experiments on the cultivation of the microörganism causing epidemic poliomyelitis, Jour. Exper. Med., 1913, xviii, 461–485.
6. Rosenow, E. C.; Towne, E. B., and Wheeler, G. W.: The etiology of epidemic poliomyelitis: Preliminary note, Jour. Am. Med. Assn., 1916, lxvii, 1202–1205.
7. Mathers, G.: The etiology of acute epidemic poliomyelitis, Jour. Infect. Dis., 1917, xx, 113–124. Nuzum, J. W., and Herzog, M.: Experimental studies in the etiology of acute epidemic poliomyelitis, Jour. Am. Med. Assn., 1916, lxvii, 1205–1208.
8. Nuzum, J. W.: Bacteriologic findings in the cerebrospinal fluid in poliomyelitis serum, Jour. Am. Med. Assn., 1916, lxvii, 1437–1439.

9. Rosenow, E. C., and Towne, E. B.: Bacteriologic observations in experimental polio-
myelitis of monkeys, Jour. Med. Res., 1917, n. s., xxxi, 175–186.
10. Rosenow, E. C.; Towne, E. B., and Wheeler, G. W.: Observations on immunity of
monkeys to experimental poliomyelitis, Jour. Am. Med. Assn., 1917, lxviii, 280–282.
11. Mathers, G., and Tunnicliff, Ruth: A reaction of immunity in acute poliomyelitis,
Jour. Am. Med. Assn., 1916, lxvii, 1935–1936.
12. Neustaedter, M., and Banzhaf, E. J.: An antipoliomyelitis horse serum, Jour. Am.
Med. Assn., 1917, lxviii, 1531–1533.
13. Flexner, S., and Amoss, H. L.: The rapid production of antidysenteric serum, Jour.
Exper. Med., 1915, xxi, 515–524.
14. Amoss, H. L., and Wollstein, W. M.: A method for the rapid preparation of anti-
meningitis serum, Jour. Exper. Med., 1916, xxiii, 403–417.
15. Fornet, W., and Müller, M.: Zur Herstellung und Verwendung präzipitierender Sera
insbesondere für den Nachweis von Pferdefleisch, Ztschr. f. biol. Techn. u. Methodik,
1908, i, 201–206.
16. Bonhoff, H., and Tsuzuki, M.: Ueber die Schnellimmunisierungsmethode von Fornet
und Müller (Präzipitine und Hämolysine), Ztschr. f. Immunitätsforsch. u. exper.
Therap., 1909–1910, Orig., iv, 180–194.   Tsuzuki, M.: Ueber die Schnellimmuni-
sierung nach Fornet und Müller (Agglutinine), Ztschr. f. Immunitätsforsch. u.
exper. Therap., 1909–1910, iv, 194–209.
17. Gay, F. P., and Fitzgerald, J. H.: An improved rapid method of producing precipitins
and hemolysins, Univ. California Pub. in Pathology, 1912, ii, 77–82.   Locke, E.:
A rapid method of producing bacterial agglutinins, Univ. California Pub. in Path-
ology, 1912, ii, 91–96.

THE TREATMENT OF EPIDEMIC POLIOMYELITIS WITH IMMUNE HORSE SERUM*

Preliminary Report

E. C. ROSENOW

In a previous report[1] it has been shown that the serum of a horse which had been immunized with streptococci isolated from the central nervous system of monkeys paralyzed with virus, had the power to neutralize virus in vitro, and to prevent poliomyelitis in monkeys following intracerebral inoculation of active virus. Moreover, this serum appeared to have a curative effect in the experimental disease in monkeys after the symptoms had begun.

Opportunity to test the effect of this serum in patients presented itself during the present epidemic of anterior poliomyelitis at Davenport, Iowa, and surrounding community. The routine procedure consists of making a spinal puncture for diagnostic tests and for relief of abnormal intraspinal pressure, and of injecting the serum. From 5 to 30 c.c. of spinal fluid are allowed to escape, depending on the age of the patient and the amount of pressure. The fluid is made to flow slowly because it is believed that rapid withdrawal might be harmful. The cell count and Noguchi's globulin test are made at the bedside, and if positive, the injection of serum is given at once. The serum is activated with complement by adding one part of fresh guinea-pig serum to nine parts of the immune serum and incubating at 37 C. for one hour. It is then diluted with equal parts of 0.85 per cent salt solution. The diluted serum is injected slowly into a suitable superficial vein not later than thirty-six hours after activation. Approximately 2 c.c. of the mixture are injected per minute of time. The dose is varied according to the age of the patient and severity of the symptoms. Babies from about one to two years of age are given from 3 to 7 c.c. of serum at each injection, that is, 6 to 14 c.c. of the mixture; children from two to five years of age from

7 to 10 c.c., and older individuals from 10 to 20 c.c.   The injections are repeated in from eight to twenty-four hours if necessary.

Every patient in whom the diagnosis is definite and the disease still active, is given injections of serum irrespective of the severity of symptoms.   Altogether 44 patients have been treated.   Of these 9 died, a mortality of 20 per cent.   Of the 9 fatal cases, 6 were moribund, or in a dying condition from respiratory failure at the time the serum was given, and hence should not be included as treated cases.   Of the 38 patients in whom there was sufficient time for the serum to act, 3 died, a mortality of 8 per cent.   One of these was a baby eleven months old, semicomatose, with spasms eight days after onset of the illness when the serum was first given.   One, a boy two years old with cyanosis, marked tremors, high fever, severe gastro-enteritis, and beginning respiratory paralysis on the second day at the time of the first injection; and one, a girl eleven years old, with high fever and paralysis of the face on the third day, when the first dose of serum was given.   Of these 38 treated cases, 22 showed definite paralysis when the treatment was begun, and 16 were in the preparalytic stage.   Excepting the 3 fatal cases in the former group, paralysis appeared to be arrested in all but one, a boy five years of age, in whom a moderate paralysis developed in the left leg, the first injection of serum being given on the second day of the disease.   All of the 16 cases treated before paralysis had begun recovered without paralysis.

These results are in sharp contrast to the 23 untreated cases which occurred during this epidemic, of which 9 patients died, a mortality of 35 per cent.

The apparent good effects from the injection of serum are often striking.   The headache, nervousness, restlessness, and tremor often disappear promptly.   The temperature and pulse-rate are lowered.   A beginning paralysis often disappears in an astonishingly short time.   A rapidly progressing paralysis is often arrested and improvement is unusually rapid.   The postparalytic pains do not appear or are comparatively mild.   It is believed that the unactivated serum would do good, and that intraspinal injections might be given with benefit, but since the activated serum and intravenous injections have given the best results in monkeys, and are yielding such splendid results in patients, I have not felt justified in changing the method.   Intravenous injections in this epidemic appear especially desirable because the gastro-intestinal symptoms are so pronounced.

It is, of course, realized that many more patients must be treated before conclusions can be drawn as to the exact value of this treatment. Of its harmlessness and apparent good effects there can scarcely be any question.   There is on hand enough serum to treat approximately 800 patients.   Suitable quantities will be sent gratis on request to physicians or laboratories for reports of cases in localities where poliomyelitis now exists in epidemic form.

I wish here to express my very great appreciation for the courtesies extended me in the use of the Pathological Laboratory at Mercy Hospital, Davenport, Iowa, and of the splendid coöperation of the physicians making it possible to treat the disease in the early stages.

REFERENCE

1. Rosenow, E. C.: The production of an antipoliomyelitis serum in horses, Jour. Am. Med. Assn., 1917, lxix, 261.

RESULTS OF STUDIES ON EPIDEMIC POLIOMY-ELITIS*

E. C. ROSENOW

I accepted the invitation to present before the American Public Health Association the results of my studies on poliomyelitis with some hesitation, since the details of much of the work have not yet been published. However, I consented to do so in the belief that it might lead to a better and a wider understanding of the disease in its various manifestations.

Ever since Landsteiner and Levaditi and Flexner and Lewis demonstrated the virus of poliomyelitis to be filtrable, bacteria of ordinary size growing on ordinary mediums under aërobic conditions have been considered of little or no etiologic importance in this disease. My own studies were undertaken to determine, by methods used in other diseases, whether there is present in the infection atrium (tonsils, throat, adenoids, etc.), and in the involved tissues themselves, bacteria of the above type which might localize electively in the central nervous system of animals.

From July 21 to August 10, 1916, there were studied 7 typical cases of epidemic poliomyelitis which occurred in Rochester. The cultures obtained from material expressed from the tonsils, injected intravenously in young animals (chiefly guinea-pigs and rabbits), was followed by flaccid paralysis in some of the animals in each case. On the basis of these striking results I decided to go to New York where these experiments might be repeated and where postmortem material might be available. From August 12 to October 6, during the height of the epidemic in New York, in conjunction with Dr. E. B. Towne and Dr. G. W. Wheeler, the above results were verified with tonsil strains and extended to strains from brain and cord. At a later date, by the use of similar methods, similar results were obtained with brain and cord

strains by Mathers, and Nuzum and Herzog.   The extirpated tonsils of patients who were not convalescing as they should be, and particularly those obtained in fatal cases, were found to contain peculiar abscesses in which this streptococcus was present in enormous numbers.   Cultures of the brain and cord in each of 12 fatal cases yielded the identical streptococcus which also showed a marked tendency to invade the central nervous system of animals.   The same organism has been isolated from the brain and cord of every monkey paralyzed either with fresh human virus, with glycerinated human virus, glycerinated monkey virus, or with filtrates of virus.   Moreover, it has been repeatedly isolated from glycerinated human and monkey virus months after glycerination and from filtrates of virus which were proved to produce poliomyelitis in monkeys.

Control cultures in numerous normal guinea-pigs and rabbits, and in inoculated monkeys dying of ulcerative colitis, showed streptococci in small numbers in a few instances only, and these were either culturally or immunologically different from those isolated from poliomyelitic tissues. On blood-agar plates the organism produces fine, dry, non-adherent, slightly green colonies, at times showing in forty-eight hours a narrow hazy zone of hemolysis.   On this medium, as well as in ascites-dextrose agar, the organisms are quite uniform in size and resemble pneumococci, but are usually smaller and free from demonstrable capsule.   In tall tubes of ascites-dextrose broth with or without sterile tissue there is usually an early diffuse turbidity, or there may be a flocculent growth which collects along the side of the tube and gradually settles to the bottom.   Early smears show short chains of diplococci resembling pneumococci, a smaller number of medium-sized cocci in pairs, and occasionally very small coccus forms.   In ascites fluid containing sterile tissue the growth appears as a slight haziness near the bottom of the tube on the fourth or fifth day when cultures are made of human or animal brain and cord.   In a very few instances the early smears have shown the tiny globoid bodies described by Flexner and Noguchi in apparently pure culture, but usually there have also been a certain number of medium-sized diplococci in short chains, which Flexner and Noguchi and others have considered contaminations.   Transplants from one to another of these liquid mediums disclose a marked tendency of the microörganism to change to the form characteristic of the medium in which it is planted.   Thus, an apparently pure culture of the very small globoid bodies in ascites tissue fluid when transferred to ascites dextrose tissue broth grows out rapidly, often in twenty-four hours, into the char-

acteristic polymorphous streptococcus. Similarly a transplant from broth to ascites fluid tends to grow slowly smaller.

The mechanism by which the large forms become small has been demonstrated. Cultures of Berkefeld N filtrates of emulsions of brain and cord of rabbits dead from paralysis following intravenous injection, with suspensions of broth cultures showing only the large forms, have repeatedly grown out in this characteristic form in each of these culture-mediums. Cultures showing the small forms have been filtered, and cultures of the filtrate have grown, but no growth has been obtained from filtrates of cultures of the same strains showing only large forms. The same emulsions filtered through dense porcelain candles have, with few exceptions, always been sterile.

In all the liquid mediums during the early days of growth, chains are often found in which there are single members of all sizes and shapes— large diplococci, large coccus forms, small diplococci, and small coccus forms. Frequently, elongated forms resembling diphtheroid bacilli or distinct rods are found in chains which are made up chiefly of typical diplococcus forms. This has occurred in strains that have been fished successively several times from single colonies of shake and plate cultures, and in those from filtrates, and are therefore believed to be variations of one organism and not contaminations.

The importance of immunologic studies with this pleomorphic streptococcus to determine the exact relation between this organism and virus as generally understood was recognized very early in the work. Recently isolated cultures were found to protect monkeys against virus.[9] Horses have been immunized, one with cultures isolated a short time previously from brain and cord of monkeys paralyzed with virus, and another with those isolated from the cases of human poliomyelitis which occurred last summer.[6] By means of these serums it has been determined that the strains isolated from human poliomyelitis and experimental poliomyelitis in the monkey (following injection of virus) are immunologically identical, both being cross-agglutinated specifically in high dilution by these serums respectively. Moreover, by selecting particularly sensitive strains with the immune horse serums it has been found that the serum of patients and monkeys having recovered from poliomyelitic attacks likewise agglutinated specifically the strains both from human and monkey poliomyelitis. The serum from the horse (Horse 1) injected from November 2, 1916, to May 10, 1917, with recently isolated

strains from monkeys was found to have definite protection and apparently curative power against virus in monkeys.

The effect of this serum was tested recently on 56 cases of human poliomyelitis during the epidemic at Davenport, Iowa. The technic of the preparation and administration of the serum, the diagnostic tests and the results obtained in 44 cases, have already been published. The details of the cases will appear later.[7] Suffice it to state that all the 16 patients who received the serum before paralysis had set in recovered promptly without paralysis. All the 17 patients with slight paralysis who received the serum likewise recovered. In only one of these did the paralysis extend, and then but slightly. In all the others paralysis was arrested and recovery took place promptly. All will undoubtedly have complete restoration of function. Twenty-three patients had advanced paralysis when serum treatment was begun. Ten of these died, giving a mortality rate of 18 per cent. Seven were practically moribund when the serum was given, and hence cannot be counted against the serum. In the 3 remaining fatal cases the serum had time to act. One was a baby, eleven months old, semicomatose, with spasms eight days after the onset of the illness, when the serum was first given. One, a boy two years old with cyanosis, marked tremors, high fever, severe gastro-enteritis, and beginning respiratory paralysis on the second day at the time of the first injection; and one, a girl eleven years old, with high fever and paralysis of the face on the third day when the first dose of serum was given. Hence this makes a mortality of about 6 per cent in sharp contrast to the 9 deaths which occurred in 23 untreated cases—a mortality rate of 35 per cent.

The epidemic in Davenport differed from those studied last year in Rochester and in New York in that gastro-intestinal symptoms and the symptoms referable to the central nervous axis were more pronounced, and that the mortality rate was higher in the cases in which serum treatment was not used. The results obtained last year with reference to the tonsils as affording an important place of entrance for the infection have been verified and extended. Glandular enlargement was found in many cases to be in proportion to the evidence of infection in one or both tonsils, as obtained on examination of the patient and on dissection of the tonsils after death.

The identical streptococcus has been found in enormous numbers in the characteristic abscesses in tonsils. It has been isolated from brain and cord in all fatal cases in which cultures were made, and from mon-

keys paralyzed with the new virus. As occurred last year, injection of recently isolated cultures into animals was followed by characteristic localization. Very little or no evidence of contact-infections could be found. The occurrence of more than one case in a family was rare and in such instances the attacks were close together. A careful study of the state of health of others in the famliy in which typical cases occurred, and of the general health of the community at the time of the epidemic, the details of which will appear subsequently, brings with it the conviction that a large proportion of the population harbored the infection and that only one case out of the usual number (1 in 600 to 1 in 1000 inhabitants) developed the typical syndrome recognized as poliomyelitis. From the studies detailed here the infection appears to be due to a form of streptococcus (using this term in the broad sense) having peculiar localizing powers. In this connection it is of interest to note that the incidence of poliomyelitis in families and the community at large during epidemics in summer is about that of rheumatic fever or pneumonia during the colder seasons, when the more virulent streptococcal respiratory and tonsillar infections occur in epidemic form.

REFERENCES

1. Flexner, S., and Lewis, P. A.: The nature of the virus of epidemic poliomyelitis. Jour. Am. Med. Assn., 1909, liii, 2095.
2. Flexner, S., and Noguchi, H.: Experiments on the cultivation of the microörganism causing epidemic poliomyelitis. Jour. Exper. Med., 1913, xviii, 461–485.
3. Landsteiner, K., and Levaditi, C.: La transmission de la paralysie infantile aux singes. Compt. rend. Soc. de biol., 1909, lxvii, 592–594.
4. Mathers, G.: Some bacteriologic observations on epidemic poliomyelitis. Jour. Am. Med. Assn., 1916, lxvii, 1019.
5. Nuzum, J. W., and Herzog, M.: Experimental studies in the etiology of acute epidemic poliomyelitis. Jour. Am. Med. Assn., 1916, lxvii, 1205–1208.
6. Rosenow, E. C.: The production of an antipoliomyelitis serum in horses. Jour. Am. Med. Assn., 1917, lxix, 261–265.
7. Rosenow, E. C.: The treatment of epidemic poliomyelitis with immune horse serum. Preliminary report. Jour. Am. Med. Assn., 1917, lxix, 1074–1075.
8. Rosenow, E. C., and Towne, E. B.: Bacteriologic observations in experimental poliomyelitis of monkeys. Jour. Med. Res., 1917, xxxvi, 175–186.
9. Rosenow, E. C., Towne, E. B., and Wheeler, G. W.: Observations on immunity of monkeys to experimental poliomyelitis. Jour. Am. Med. Assn., 1917, lxviii, 280–282.
10. Rosenow, E. C., Towne, E. B., and Wheeler, G. W.: The etiology of epidemic poliomyelitis. Preliminary note. Jour. Am. Med. Assn., 1916, lxvii, 1202–1205.

THE SURGICAL TREATMENT OF INFANTILE PARALYSIS*

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The surgical or operative treatment is only a small part of the after-care of the patient afflicted with infantile paralysis. After the acute symptoms have subsided, in a vast majority of instances there is a flaccid paralysis to deal with. The treatment should be directed so that the paralyzed muscles are held in the position of physiologic rest, the position most advantageous for the return of power and for the prevention of deformity. It is my purpose in this paper to consider only those operative procedures that are more or less standardized, and briefly to outline their usefulness and possibilities. The postfebrile period and pre-operative measures demand, first, as stated above, physiologic rest for the paralyzed muscle, and second, when signs of return of power are present, graduated exercises, great care being taken not to overwork the muscle. Lovett, in his recent and most excellent investigations, has shown that overwork of a partially paralyzed muscle may delay or even completely prevent the return of power. We appreciate the significance of this warning when we realize that only one muscle in ten affected is completely paralyzed. Carefully graduated exercises and trained massage undoubtedly conserve and increase the residual muscle-power.

In the minds of the laity electricity and braces are well fixed as therapeutic agents for the treatment of infantile paralysis. Electricity may be somewhat summarily dismissed as a factor of no importance, for although it cannot be said positively that it does damage per se, we may safely conclude that its use has resulted in a great deal of harm because of excessive application and the exclusion of other valuable measures by the laity and practitioners of various cults. Electricity should be given only by those who are appreciative of its relative values in the treatment of infantile paralysis, and who are trained in using it. Braces have a

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well-defined use, but it must be constantly kept in mind that they are to prevent and not to correct deformity. They should be as light as is consistent with strength and as simple and as cheap as possible. The same brace should not be worn night and day, but a night brace should be provided. The latter is often made of plaster-of-Paris in the form of a gutter-splint or half cast.

There comes a time when the patient ceases to improve even under the best direction and treatment. It is at this stage that operative measures are to be considered.

Fig. 270.—(197216.) Genu recurvatum (backward curvature of the knee-joint), which could have been prevented by lock braces on the knee.

As the disease affects the nervous system, the transferring of fibers from a healthy nerve into a paralyzed nerve-trunk has been advised by some, notably Stoffel, but the results have been anything but satisfactory. The technical difficulties of the operation are great and the surgeon must be very carefully prepared before undertaking it, for a most intimate anatomic, and one might say histologic, knowledge is necessary for its successful accomplishment. The neurotization of the muscle is attempted by anastomosing a healthy nerve to a paralyzed nerve, thus sending healthy fibers from a normal nerve-trunk through the sheath of the paralyzed nerve to the paralyzed muscle. Neurotization of the paralyzed muscle by opening the sheath of an adjacent healthy muscle and the sheath of the paralyzed muscle, and sewing the healthy muscle-fibers to the paralyzed muscle-fibers, has also been attempted. These attempts have been clinically unsuccessful, but the experimental work has been sufficiently encouraging to warrant further investigations (Steindler and Nutt). It is generally conceded that as yet neither of these methods is to be accorded a definite place in the operative treatment.

Primarily it should be realized that the operative measures at our command are palliative and corrective, but not curative; the actual disease is past and the patient is suffering from the after-effects of an infection which strikes the cerebrospinal nervous system. Unfortunately, the location of the lesion in the anterior horns of the spinal cord precludes the possibility of any local surgical interference during the

Fig. 271.—(153225.) Talipes equinovarus paralyticus.

acute stage. We must place our hopes on prophylactic measures and the use of some kind of serum. Rosenow's convincing work leads us to expect much from such measures.

There remains to the surgeon the duty of restoring function to the paralyzed limbs by such means and methods as are at his command. A combination of unfortunate circumstances made up of the ignorance of the laity, lack of appreciation by the medical profession of the impor-

tance of maintaining physiologic rest, the extravagant claims of various cults using electricity, spinal adjustments, etc., the distance of some patients from surgical centers, and often their poor social condition allows the development in many instances of extreme deformities (Fig. 270). It is lamentable that the large majority of the operations performed for infantile paralysis are necessitated by the lack of proper attention, muscle training, massage, and the intelligent use of braces which could have been carried out from the time of the onset of the paralysis, each being used as the need arose. In the effort to restore these patients as far as possible the ingenuity of the surgeon has been taxed to the utmost.

In order to prevent foot-drop and even to give stability to joints the use of silk or artificial suspensory ligaments has been advocated, but in spite of the fact that it has been used extensively it has not secured for itself a definite place in our armamentarium. Although good results have been secured occasionally, in the majority of instances the silk has failed of its purpose.

Fig. 272.—(153225.) Showing the impossibility of correcting the deformity by the use of a brace.

Tendon transference or tendon transplantation is an extensive subject of itself. This procedure was rapidly popularized, operations were performed with no regard to physiologic or mechanical principles, and the result was only what might be expected—the operation to a large extent fell into disrepute. We now know that cases suitable for this method are somewhat rare. The muscle must be of sufficient strength so that when it is transferred it will have power to carry out its new duties, which often has to be done at a mechanical disadvantage. Many cases have been reported as successes when the only reason for calling them such was that the muscle was able to functionate feebly, but the

transposed tendon was not of the slightest practical use. In the foot, for example, there must be practically normal power in two of the three muscle-groups before the transference should be made of one of these muscles to perform for the paralyzed group. If the peroneals are paralyzed and the tibialis anticus and tendo achillis are normal (Figs. 271 and 272), the foot should first be corrected, if any deformity is present, and the tibialis anticus tendon transferred to the insertion of the peroneal or inserted into the paralyzed tendon near the insertion.

Fig. 273.—(153225.)   After operation.   Tibialis anticus split and half of it transferred to the outer side of the foot.

The tendon may be split and a portion left in the normal insertion (Figs. 273 and 274). Mechanical principles must be adhered to, and care taken that the transferred tendon is not expected to pull around a corner, so to speak. The line between the origin and the new insertion should be as straight as possible. Occasionally the extensor proprius hallucis may be inserted into the head of the first metatarsal bone or into the inner side of the foot to take up the work of the tibialis anticus. The greatest care must be taken that a foot which is already out of

Fig. 274.—(153225.)   A properly applied brace for maintaining correction.

balance is not further weakened. A very useful tendon transference has been that of the biceps or semitendinosus of the thigh into the patella. This gives greatly increased stability if not much increase in the extension power of the knee in cases of paralysis of the quadriceps femoris. In my experience transference of the peroneals to the inner side of the foot has not been of any value and in our clinic has practically been abandoned. Generally speaking, the tendon transferences have not come up to our early expectations. We are now gradually standardizing them, but there is no operation in surgery that demands more careful preoperative study and selection of cases. The patient must be studied. It is clearly useless to do a transference before the child is old enough to coöperate in the training of the muscle in its new situation after the operation. This age has been arbitrarily set at eight years.

The Whitman type of astragalectomy is perhaps the most useful operation that has been devised to treat certain deformities of the foot, notably calcaneus and calcaneovalgus, with the accompanying flail ankle. To attain the best results, the rules laid down by Whitman must be carefully adhered to.

Fig. 275. —(158344.) Flail shoulder.

The inadequacy of silk as a suspensory ligament and stabilizer led Gallie to use the distal ends of paralyzed tendons. The method is perhaps best illustrated by a concrete example, foot-drop with the accompanying valgoid deformity. Here we have to deal with paralyzed extensors. By dividing the tibialis anticus tendon just above the ankle, scarifying the glistening smooth surface, implanting it in a groove prepared in the lower end of the tibia, sewing it firmly to the periosteum with the foot held in the position of election, the tendon grows firmly

to the bone and acts as a true living suspensory ligament. Gallie has produced proof that this can be done successfully and it has been my experience that if carefully done, it is a most useful procedure. Careful technic is essential to success.

In certain cases arthrodesis is to be preferred to any other type of operation. This naturally should be used only for persons beyond the age of puberty, on whom thorough conservative measures have been tried or sufficient time has elapsed since the onset, to ascertain whether

Fig. 276.—(158344.)   Arthrodesis of shoulder-joint.

or not power would return to any of the paralyzed muscles. Unfortunately, in not a few instances in which a knee-joint has been ankylosed it was taken for granted that the quadriceps was completely paralyzed only to find that after the postoperative fixation of the entire limb, necessary to secure ankylosis, power had returned in the quadriceps. The rule holds and must be emphasized that before ankylosing any joint, the limb should be placed in the position of physiologic rest in order that we may be positive the paralysis is complete enough to warrant the operation.   Arthrodesis of the astragalus and os calcis has been advocated by

Davis for certain cases of flail ankle. Davis claims that in the majority of cases of the severe valgoid deformities this will do away with the necessity of performing an astragalectomy. The valgus is caused by the slipping action of the os calcis on the astragalus and not of the astragalus on the tibia, the astragalus being held firmly between the malleoli and no lateral motion being permitted. Arthrodesis of the astragalus and

Fig. 277.—(158344.) Plaster-of-Paris right-angle abduction splint. Post-operative.

os calcis, however, will not apply to severe late cases of calcaneous deformity.

The social status of the patient perhaps more than any other one factor determines the advisability of an arthrodesis. For example in the case of a flail knee a man or a woman working in an office might prefer a lock-jointed brace, whereas a man or a woman whose duties required much standing and walking would prefer an ankylosed joint in order to

do away with the wearing of the brace and all of its accompanying convenience. In a patient who has a useful foot and a weight-bearing hip, but a flail knee, the ankylosing of the knee is very satisfactory. So also in the case of the patient who has a good ankle and foot and a fair knee power, but a paralysis of the hip muscles, an ankylosis of the hip is of great benefit, placing the thigh at an angle of flexion of 40 degrees with slight abduction, and thus allowing the patient to walk with only a slight limp while still permitting him to sit down in an ordinary chair. Oftentimes a shoulder paralysis is extremely inconvenient (Fig. 276). When the deltoid muscle is paralyzed but the scapular muscles are working, an ankylosis of the humerus to the scapula at a right angle gives a very useful arm. Immediately following the operation a plaster-of-Paris cast or brace must be worn (Fig. 277), the arm being held at right angles to the trunk until the ankylosis is firm. When the ankylosis is complete, the arm may be allowed to drop gradually to the side. It will then be found that

Fig. 278.—(158344.) Showing the ability of the patient to abduct the arm to right angle and to touch the opposite shoulder, after arthrodesis.

the scapular muscles will enable the patient to abduct the arm to a right angle, a source of great satisfaction to those unfortunates who have previously been denied this motion (Fig. 278). A flail elbow may be ankylosed at a right angle, and this is particularly gratifying if the patient has good forearm muscles so he can use the hand. When the hand is paralyzed, however, an operation of any sort is not satisfactory, as a rule. The opportunity for transferring tendons in the case of hands is extremely

limited, the motion of the fingers being so specialized and intricate that it is very hard to reëducate the muscles. In wrist-drop, transference of the flexor carpi ulnaris into the extensors has been advised.

Before undertaking any operative steps in the lower extremities the line of weight-bearing must be carefully investigated to see if there are any gross variations. Hoke has called our attention to the fact that at times there is associated a more or less rotary deformity in the femur and tibia, the correction of which will reëstablish the correct weight-bearing line, and the increased stability thus secured is often quite surprising.

Conclusions

1. Operations for infantile paralysis demand a careful consideration of the social status of the patient as well as careful testing of the muscle function.

2. Operative procedures are to be undertaken in cases of infantile paralysis only after it is certain that power will not return to the paralyzed muscles.

3. The use of silk as artificial ligaments is not advisable.

4. Tendon transference or transplantation operations are to be undertaken only when the muscle to be transferred is powerful enough to carry out its new duties, and should not be performed when more than one group of muscles in the limb is paralyzed.

5. Arthrodesis is an operation to be decided on from the extent of the paralysis and the social status of the patient.

REFERENCES

1. Davis, G. G.: Treatment of the paralysis following poliomyelitis. Am. Jour. Orth. Surg., 1916, xiv, 664–669.
2. Gallie, W. E.: Tendon fixation for deformity resulting from partial paralysis. Ann. Surg., 1915, lxi, 94–95.
3. Gallie, W. E.: Tendon fixation in infantile paralysis. A review of one hundred and fifty operations. Am. Jour. Orth. Surg., 1916, xiv, 18–29.
4. Hoke, M.: Correction of skeletal defects of lower extremities resulting from poliomyelitis. Presented before the Section on Orthopedic Surgery of the American Medical Association, New York, June 6, 1917.
5. Lovett, R. W.: A plan of treatment in infantile paralysis. Jour. Am. Med. Assn., 1916, lxvii, 421–426.
6. Lovett, R. W.: The after-care of poliomyelitis as a public problem. Jour. Am. Med. Assn., 1917, lxviii, 411–414.
7. Nutt, J. J.: Neurotization of paralyzed muscle; a clinical and laboratory study. Jour. Am. Med. Assn., 1917, lxix, 2082–2085.
8. Rosenow, E. C.: The etiology of epidemic poliomyelitis. Jour. Am. Med. Assn., 1916, lxvii, 1202–1205.
9. Steindler, A.: Direct neurotization of paralyzed muscles; Further study of the question of direct nerve implantation. Am. Jour. Orth. Surg., 1916, xiv, 707–719.
10. Stoffel, A.: In Vulpius, O.: The treatment of infantile paralysis. New York, Wood, 1912, pp. 104–126.
11. Whitman, R.: A treatise on orthopedic surgery. Philadelphia, Lea, 1901.

SPINA BIFIDA—ITS OPERATIVE TREATMENT*

E. H. BECKMAN AND A. W. ADSON

There seems to be a great deal of misunderstanding among men in the medical profession in regard to spina bifida and the results that may be expected from the surgical treatment of the condition. Spina bifida should be looked upon as a hernia from the spinal canal due to an excess of pressure in that canal in intra-uterine life. Such hernias occur at the point in the canal where ossification of the vertebræ takes place at a late period of development. The ossification is at the upper and lower ends of the spine, that is, at the cervical and lumbar sacral portions. For some unknown cause, probably an excess or diminution of hormones in the blood of the mother, the choroid plexus is stimulated to secrete an excess of cerebrospinal fluid. As this excess of fluid accumulates the spinal canal bulges, thus making room for the formation of a true hernia. Such hernias, or spina bifida, as they are commonly called, are usually divided into three groups, depending for their classification on the contents of the hernial sac. When the meninges alone bulge into the sac, the hernia is known as a meningocele. When, in addition, some of the nerve-fibers or a portion of the spinal cord itself bulges into the sac, it is known as

Fig. 279.—(190,974.) Meningocele of the lumbosacral region. Child nine months old. No paralysis or destruction of the vertebra.

a myelomeningocele. If the pressure comes in the center of the spinal cord so that a hernia of the neural canal itself occurs, with bulging of the meninges, the condition is known as syringomyelocele (Figs. 279, 280, 281, and 282).

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Other evidence to support the belief that these are true hernias of the spinal canal is the fact that in so many instances there is an associated hydrocephalus. An idea seems to

Fig. 280.—(189,212.) Meningocele of the occipitocervical region. Child nine months old. No paralysis or destruction of the vertebra.

prevail in the medical profession that the excessive fluid is secreted in the sac of the spina bifida and that if, by operative interference, this sac can be obliterated the excess of cerebrospinal fluid will cease and the patient be improved thereby. This idea is entirely erroneous. The fluid is normal cerebrospinal fluid secreted, in all persons, by the choroid plexus, so that any operation on the spina bifida sac would have no more influence in preventing the excessive secretion than the removal of a large umbilical hernia has on the secretion of the ascitic fluid in a person afflicted with this disorder. The influence that operative interference may possibly have in a case of spina bifida associated with hydrocephalus is to prevent the safety-valve action due to the elasticity of the walls of the sac and consequently increase the hydrocephalus.

The sooner it is learned that patients with hydrocephalus and a rapidly growing spina bifida are not surgical cases, the sooner will the operative mortality drop. To cure the hydrocephalus without operation should be the first effort in the treatment of such a case. There is no accepted treatment for the condition, but probably the most rational procedure is to puncture the corpus callosum. Marked improvement in hydrocephalus has recently been reported following this procedure. We have per-

Fig. 281.—(191,602.) Myelomeningocele of the lumbosacral region. Man thirty-nine years of age. Bladder involvement, but no destruction of the vertebra.

sonally seen considerable improvement in several cases, but they have not been under consideration long enough to prove that cure has been effected.

Another very prevalent erroneous impression is that when these persons have paralysis of the lower extremities with loss of control of the bladder and bowels an operation may cure them. Physicians should be taught that when there is paralysis it is due to the fact that some of the nerves or an entire portion of the lower end of the spinal cord that should supply the lower extremities and furnish innervation to the pelvis, pass out into the spina bifida sac and often terminate there. Consequently removal of these nerve-twigs and portions of the spinal cord from the hernial sac with replacement into the spinal canal has almost no effect on the patient's condition. The only cases in which such improvement can be expected are the few in which the nerve bulges into the spina bifida sac, becomes adherent there, and again enters the spinal canal. Freeing such a nerve from its adhesions may reëstablish its function; on the other hand, it may also interfere with function.

Fig. 282.—(152,498.) Syringomyelocele associated with hydrocephalus. Child eight months old. Involvement of the bladder, bowels, and the lower extremities.

In our series of cases there has not been an instance in which a child having paralysis before operation completely recovered the use of the extremities after the operation. There have been, however, a number of instances in which the sphincter control of both bladder and bowel have improved or have become practically normal. This probably is due to the improvement which occurred with the child's development, and should not be attributed to the improvement following the operation.

Periodically a case is reported in which operation has been done and the bony defect in the spine closed by the insertion of a bone-graft taken from some other part of the body. This procedure is ridiculous on the face of it, since no extreme tension is needed in the cure of these cases, in which the hernial sac has become stationary. In cases in which the hernial sac is rapidly increasing, operation is contraindicated for the reason that when the hernial sac is closed, even by approximation of the soft tissues, the intracranial pressure increases so rapidly that death usually occurs within the first few days.

The bony defect due to the loss of one or two arches of the vertebræ is not a serious matter and is of little consequence since the arches to the vertebræ have no function in the support of the body-weight except for the attachment of muscles. No further explanation is needed on this point other than to mention the fact that in laminectomy cases in adults, when as many as six to eight vertebral arches have been removed, the patient sits up and walks about without any difficulty immediately after the operation. He does not know, unless told, that any bone has been removed.

The child should be thoroughly examined before any operative pro-
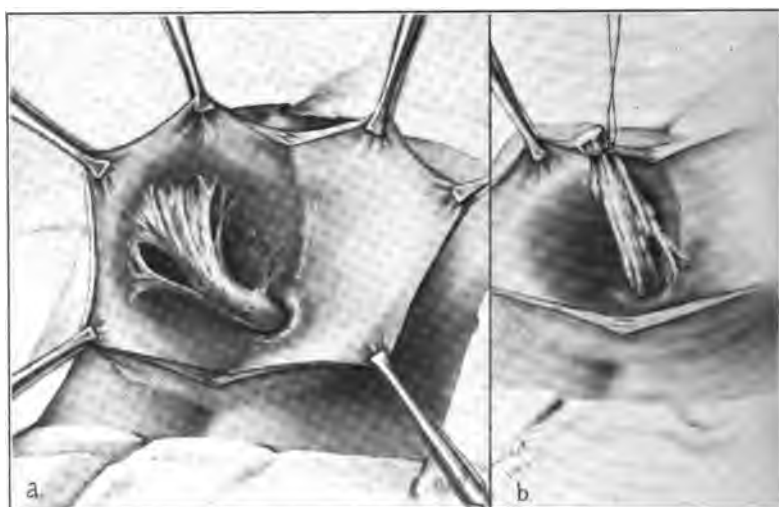
Fig. 283.—a, Incision into sac; b, freeing the cord elements from sac.

cedure is advised, to determine the general physical condition, the possibility of a hydrocephalus, and the absence or amount of paralysis. It is important to discuss the prognosis with the child's parents, as frequently they are led to believe that the operation will relieve the paralysis as well as remove the hernial sac. If the patient is old enough to understand his condition, it is advisable to make a neurologic examination, which will assist in determining the exact amount of sensory and motor disturbance. It is also important to make a roentgen examination in order to detect bony defects, if any are present.

The most suitable time for operation on a spina bifida is when the child is from nine months to two years of age. At an earlier age the

operative mortality is very high.   After the age of nine months the child is old enough to take some nourishment besides milk and usually stands the operation very well.   However, it is not advisable to wait longer than two years, as the hernial sac is apt to become very large and this increases the risk of its being ruptured as the child is up and about and may slip away from the mother's care.

It has been our experience that adults with spina bifida have been poor operative risks.   In the first place, the tissue around and in the hernial sac is more or less macerated and mildly infected.   It is difficult
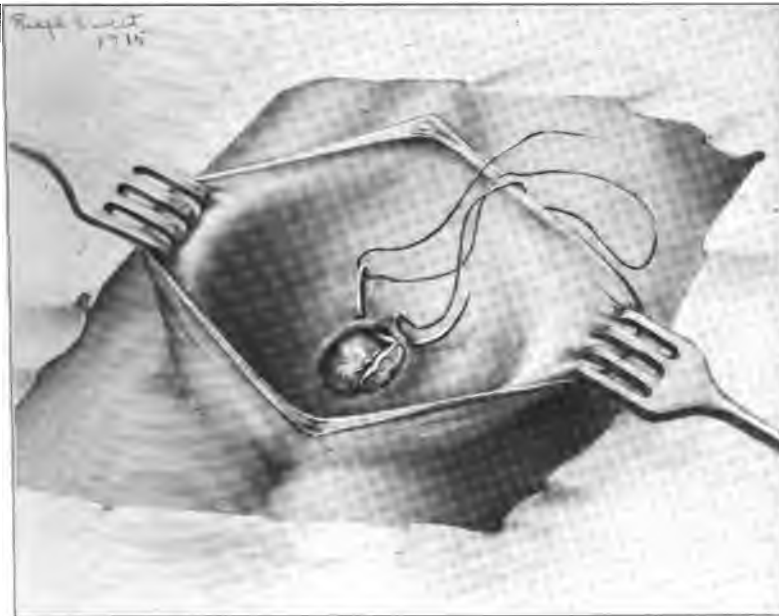
Fig. 284.—The cord reduced; the first row of sutures being inserted.

to cleanse and keep sterile, besides being very indolent in its regeneration; consequently the primary healing of skin-flaps following operation rarely occurs regardless of the precautions taken not to constrict the pedicles of the skin-flaps.   Usually the necrosis which follows an operation takes place not only in the skin-flap, but also in the tissue at some distance from the operative incision, possibly due to some atrophic disturbance which necessitates healing of the wound by granulation.   When this necrotic condition is present, infection is very apt to develop and in turn give rise to meningitis.   If the meningitis remains local, the patient may

continue to improve and eventually have an excellent result, but often the meningitis ascends and becomes cerebrospinal in type, ending in death.

In regard to the hydrocephalus associated with spina bifida, it is of great importance to ascertain whether or not hydrocephalus is or has been present during the development of the child. Operating in cases of spina bifida in which there is also hydrocephalus gives a mortality of about 50 per cent. This is due to the increased pressure that comes
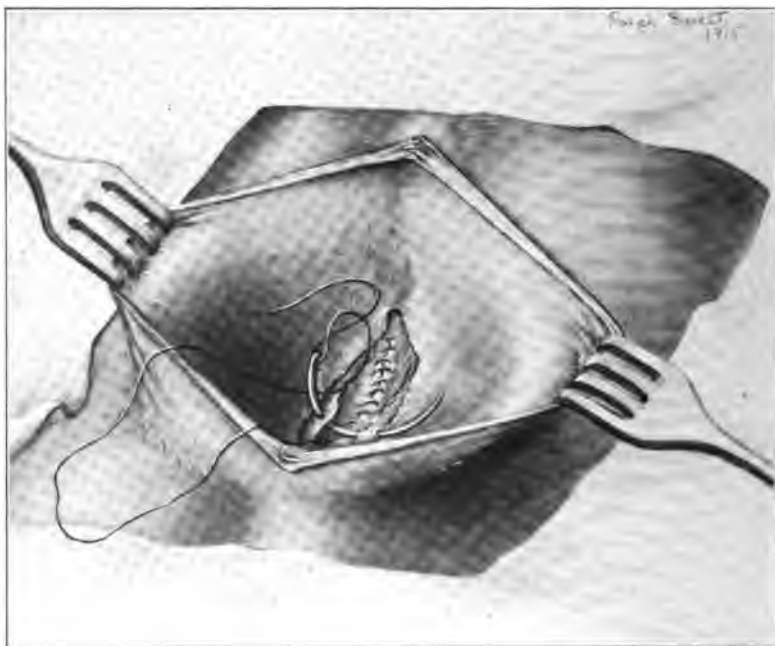
Fig. 285.—The first row of sutures completed. The incision through the wall of the sac above the first row, the second row of sutures being placed approximate to the wall of the sac.

from the removal of the sac, inasmuch as the sac has acted as a safety-valve during the development of the hydrocephalus. We have advised against operating on the spina bifida until the hydrocephalus becomes stationary, which in some instances has occurred within a year or two. If the hydrocephalus continues to develop, operating on the spina bifida should not be contemplated. In a few instances a puncture of the corpus callosum has been done prior to operating on the spina bifida. We have been successful also in slipping a drain of silk threads into the opening made in the corpus, which acts as a wick and causes a complete col-
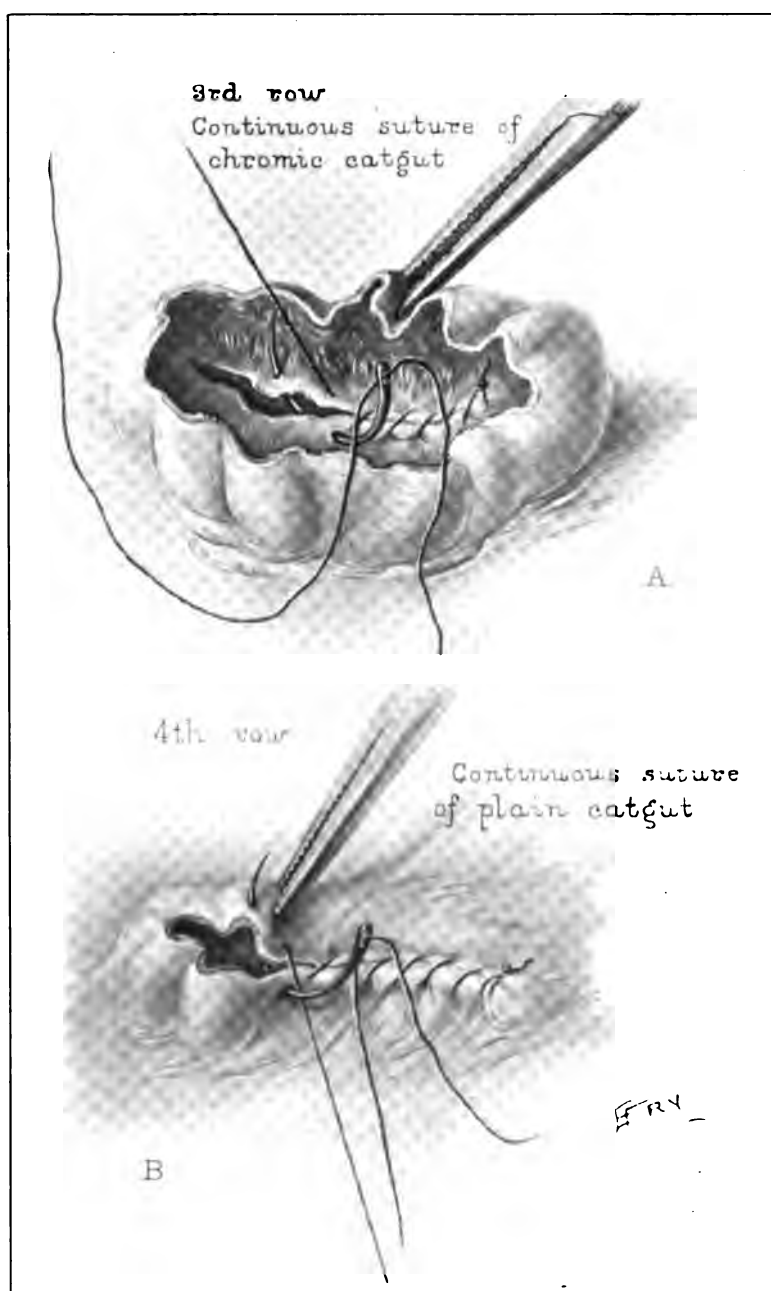
Fig. 286.—The closure of lumbar fascia after the removal of the redundant skin of the sac (A). The closure of the skin with a continuous plain catgut suture (B).

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lapse of the head with marked diminution in size and tensity of the spina bifida. The repair of the hernial sac is done ten days after the puncture of the corpus callosum.

Sufficient time has not elapsed since the treatment of the cases under our observation to give any accurate data in regard to the ultimate results, but the patients made satisfactory recoveries while in the hospital. There was no operative mortality.

The hernial sac should be carefully inspected, and if there is any abrasion or maceration of the tissue and infection or leakage of the spinal fluid, it will be well to care for these conditions before operating. It is not advisable to operate on the sac if it is draining spinal fluid, as

Fig. 287.—Sealing the wound with the tincture of benzoin on cotton.

the pressure is greatly increased immediately following the operation and sudden death may ensue. It is better to permit the opening to close spontaneously, as it frequently does, and allow the sac to bulge, thus making intracerebrospinal pressure gradual instead of sudden. Occasionally the pressure within the sac is very tense, and in such instances it is well to draw off an ounce or two of the fluid to relieve the pressure and to observe the effect it has on the child. If it is possible to drain the spina bifida several times prior to operation, this will tend to reduce the severe shock that comes when the sac is excised. If the spina bifida has many abrasions or if the tissue is macerated, it is well to cleanse with dilute alcohol and follow this by dressings of a weak alcohol-iodin

solution (1 part iodin to 100 parts alcohol—60 per cent), changed two or three times a day.

OPERATIVE TECHNIC

Ether is the anesthetic most commonly used. The patient is placed on the abdomen with the head 12 inches lower than the spina bifida sac, so that when the hernial sac is opened, the fluid within the ventricles will not drain into the spinal canal. The skin is prepared in the usual way with benzin and iodin. The operation used by us differs from the one generally used for spina bifida in that we open the sac longitudinally to its full length so as to expose the opening over the spinal canal and the contents of the sac. This exposure will show whether or not there are nerve-elements present and if so, make it possible to treat them. In the old type of operation in which the sac was dissected free without opening, this distinction was not possible during the course of the operation.

If the hernial sac is a simple meningocele, it is closed by three rows of chromic catgut. If the spina bifida is a myelomeningocele (a sac containing nerve-elements), the nerve-fibers are divided close to their exit from the point in the spinal canal and replaced within the spinal canal together with the spinal cord before a closure is made (Fig. 283). If the sac contains a part of the spinal cord itself, it then becomes necessary to close the opening superficially to the cord structures. It is not advisable to divide the cord-fibers, as many of these will bulge into the sac and then return to the spinal canal and continue in their normal course.

The first row of sutures (No. 0 chromic catgut) is placed in the dura lining the sac, but very low, so it will come on the same level as the lamina and approximate the edges of the dura over the opening of the spinal canal. The second row of sutures (No. 1 chromic catgut) is placed immediately above the first row and catches the fascia external to the dura. Before the third row (No. 1 chromic catgut) is placed, the dura covering the sac is divided so that the freshly cut edges are brought together and the fascia planes are approximated over the dura. Following this the redundant skin is excised and the skin-edges are approximated by a running suture of plain catgut (Figs. 284, 285, 286, and 287).

The wound is sealed with a cotton and collodion dressing and covered with gauze and adhesive, since it is difficult to keep the dressings clean in the case of young children. The patient is then taken from the oper-

ating room and placed on the abdomen on a pillow for the first twenty-four hours, with the buttocks fully six inches higher than the head. At the end of this time the child is permitted to lie on its side with the buttocks higher than the head. If the child is still nursing, the mother should lie on the bed beside it so that in nursing the position will not be changed. The Trendelenburg position is maintained for a week, then a flat position for two or three days. After this the child is allowed to sit up for from ten to fifteen minutes at a time, two or three times a day, the length of time being gradually increased as convalescence progresses until the patient is dismissed on the twenty-first day. Dressings may be changed about three times during the convalescence at the hospital. In a child the wound usually heals by primary intention.

Conclusions

1. Spina bifida is caused by increased cerebrospinal pressure rather than by bony defects in the arches of the vertebræ.

2. The age of patients most suitable for operation is from nine months to two years.

3. At the time of operation the spina bifida should be free from infections which may be due to abrasions of the skin or leakage of the spinal fluid.

4. As a general rule, paralysis associated with the spina bifida remains unchanged by the operation.

5. Spina bifida associated with hydrocephalus should not be operated on until the hydrocephalus becomes stationary or the pressure is relieved by some operative procedure.

6. It is not advisable to operate on adults unless they are having serious trouble, since the mortality will be high because of the frequency of necrosis of the skin-flaps and of meningitis.

THE ROENTGENOLOGIC DIAGNOSIS OF PRIMARY CARCINOMA OF THE LUNG*

F. B. McMAHON AND R. D. CARMAN

Primary carcinoma of the lungs and bronchi is a rare condition, and one in which it has been very difficult to make a diagnosis clinically. The larger number of cases reported have been taken from postmortem data and many of them were incorrectly diagnosed or overlooked during life.

In the roentgenologic examination of the chest there is a group of findings associated with primary pulmonary carcinoma that up to this time have not been fully recognized and accorded their true worth. The roentgen examination may early point to a lesion in the chest, thus making it possible, except in the very early and atypical cases, to make a definite diagnosis of primary carcinoma of the lung.

From a brief review of the literature it appears that up to this time there have been 428 authentic case reports of primary carcinoma of the lung. The most complete and excellent monograph on the subject has been written by Adler,[1] who collected 374 definite cases and several others which, though questionable, bore sufficient evidence to cause him to put them in a doubtful column.

The pathology of primary pulmonary carcinoma is most interesting. The rarity of the disease is somewhat unusual, since in the lungs and bronchi there is such a preponderance of tissue of epithelial structure. There are three types of epithelial cells: The columnar epithelium lining the bronchi and larger bronchioles, the flattened or cubical epithelium lining the alveolar spaces, and the glandular epithelium found in the mucous glands. The endothelial cells lining the pleura may also be mentioned as a possible source of primary carcinoma of the lung, but will not be discussed in this paper. In most instances the carcinomas originate from the columnar cells lining the larger bronchi. The favorite

site of origin is said to be in the second or third division of the main bronchus, but any portion may be first involved. The primary nodule enlarges, invades the bronchial wall, and extends out into the smaller bronchi and into the parenchyma of the lung. The bronchial lymph-glands are usually involved, but numerous cases are on record in which they showed no evidences of metastases, although both lungs were affected. There seem to be no established data in regard to the frequency and the favorite sites of metastases outside the thoracic cavity, unless it be the axillary and cervical lymph-glands. The liver is not often involved. Many cases have been reported in which there were no metastases, but at autopsy both lungs have been found extensively infiltrated with cancer cells. The brain may be mentioned as a probable, and at times the only, site of metastasis in primary lung carcinoma.

Grossly there are three types of primary carcinoma of the lungs and bronchi: The infiltrative, the miliary, and the mixed types. The infiltrative type is reputed to be the most common. The condition starts in one of the larger bronchi as a nodular tumor of varying size. It penetrates the wall and invades the lung along the bronchi and bronchioles, the alveolar walls, and air-spaces by way of the blood-vessels and lymphatics, by direct extension, by gravity, and by aspiration. A single lobe may be affected, usually the lower, or there may be massive areas involving parts of both lungs. In the miliary type the nodules are very numerous, two to ten or more times the size of macroscopic miliary tubercles, they have a more or less symmetric and diffuse distribution throughout both lungs, and are found far out in the periphery as well as in the central parts. The pleura may be involved with carcinoma or with simple chronic inflammatory changes. The tumors are round in form, grayish-white in color, invasive in character, not sharply demarcated from the surrounding lung tissue, and firm on section. Several of them may coalesce to form larger, irregular nodules. Degeneration and central necrosis sometimes occur, leading to caseation and cavity formation. The mixed type presents both the infiltrative and the miliary forms in the same case. In addition to a large and hard wedge-shaped or nodular area in one or more lobes, the remainder of the lung is diffusely studded with miliary nodules varying in size and number, depending on the duration of the disease.

The symptoms are variable and not diagnostic, though sometimes suggestive. The age incidence of the disease is similar to that of all

malignancies. Males are more frequently affected. Cough is an early symptom; it is usually slight, but constant and distressing. Expectoration, if any, is moderate in amount: it consists chiefly of mucus and at times may be blood-stained. Hemoptysis is common, but the quantity of blood is small. Inspiratory dyspnea comes on early, is nearly always present, and is exaggerated by exertion. Hoarseness and change of voice from pressure-paresis of one or both vocal cords are common. Pain is a prominent, but not early, symptom. It is associated with substernal pressure symptoms or pleural involvement. Pressure may give rise to dysphagia. Weight loss and weakness are pronounced and progressive. A rise of temperature of 0.5° to 1° is usual; chills and sweats are rare. The infiltrative type runs a longer course than the miliary or mixed type.

The physical findings are such as would be expected in massive or patchy infiltration and consolidation of the lung from any cause. Pleural effusion may mask these signs; on aspiration the fluid may be straw-colored, blood-stained, or darkly discolored. Engorgement of the veins of the anterior chest-wall and edema of one or both arms may be present. Enlarged supraclavicular or axillary glands are suggestive, and removal of such glands may aid the diagnosis.

In most instances the roentgen findings in primary carcinoma of the lungs are pathognomonic of the disease, and may be the first to suggest the exact nature of the pulmonary lesion. The areas of increased density, their size, shape, and position, are usually characteristic and aid in the clinical diagnosis more than most other signs. This does not imply that all other signs can be slighted or discarded, for it is by a careful collection and correlation of all the facts that a satisfactory differential diagnosis may best be established.

In the roentgen examination three types of the disease are recognizable: namely, the infiltrative, the miliary, and the mixed, which correspond to the gross pathologic groupings. For convenience each type will be discussed separately, though many characteristics are common to all. A striking feature in all types and one of considerable diagnostic importance is the absence of practically any increase in mediastinal density. The presence of extensive pleural involvement in primary carcinoma of the lung renders the interpretation of the roentgenogram correspondingly more difficult, but not impossible. The presence of large pleural effusions tends completely to mask the roentgenographic picture and to conceal the underlying and principal pathologic condition in the lung. A second roentgen examination is necessary after thora-

centesis.   Fortunately, the latter two conditions rarely occur until the terminal stages of the disease.

In the stereoscopic study of the infiltrative type of primary carcinoma of the lung the roentgenogram shows one or more areas of increased density along the roots of the larger bronchi.   The shadows are homogeneous or partially mottled.   The borders are infiltrative and not sharply demarcated.   The areas of density are wedge shaped, with the apex pointing toward the hilus, and there may be either unilateral or bilateral involvement.   The degree of density is marked but varies with the extent and duration of the disease.   Until there is extensive involvement, the process does not reach the periphery of the lung so that small areas of air-filled lung tissue may be seen between the growth and the chest-wall.   The most frequent site of this type of lesion is in one of the lower lobes.   There is always present a hazy shadow-zone surrounding the growth, due to congestion from active hyperemia or passive congestion due to mild pressure, or to both conditions.   The roentgen shadows found in this type of carcinoma of the lung at times make the diagnosis difficult.   The roentgenogram will show the presence of a lesion in the lung, but if the neoplasm is in an early stage, the areas of density may not be entirely typical of primary infiltrative malignancy.   In such cases the roentgen diagnosis can be only tentative, and if the other findings are not sufficiently corroborative, a subsequent roentgen examination should be made.

Two of the cases studied by us were of the infiltrative type.   In one (Case 176118) the roentgenogram showed the presence of a lesion in the lower right lung, the exact nature of which was doubtful until an exploratory thoracotomy and a microscopic examination were made.   In the other case the lesion was more extensive and typical of primary malignancy.   Postmortem examination confirmed the diagnosis.

In the miliary type there are innumerable regular, irregular, or conglomerate small areas of increased density extending throughout all the lobes.   Their borders are poorly defined and not sharply circumscribed from the surrounding parenchyma of the lung because of the marked infiltrating character of the neoplasm.   The process is diffuse throughout both lungs, and the areas of density are distributed as uniformly near the hilus as in the periphery of the lung.   The shadows show no tendency to be arranged in groups or clusters.   There are usually no true cavities, but there may be localized dilatations of the smaller bronchi and bronchioles, the walls of which can be differentiated from cavity formation only

by the stereoscope. Dilated bronchioles are recognized roentgeno-logically by the absence of any thickened wall. Two of the cases herein described are of the miliary type (Cases 159177 and 126018). In one the diagnosis was confirmed at necropsy; in the other no necropsy was made.

The mixed type of primary carcinoma of the lung includes a combination of the infiltrative and the miliary forms. In this type are found poorly circumscribed, homogeneous, or slightly mottled areas of increased density in one or more parts of the lung, and multiple smaller areas of increased density similar to those found in the miliary type, diffusely studding the entire remaining portions of both lungs. Two of the cases (Cases 160751 and 109685) were of this type. In both, the diagnosis was confirmed by a postmortem examination.

The differential diagnosis of primary carcinoma of the lung must be made from a large number of other pathologic conditions found in the thorax, which in the roentgenogram may in a measure simulate carcinoma. A long and detailed description of each is unnecessary here, but the salient and important points concerning the more confusing conditions are as follows:

Bronchiectasis may be confused with the infiltrative type of primary pulmonary carcinoma in the early stages, or when either lesion is atypical. Moore[2] has shown, however, that in bronchiectasis the shadow is fan-shaped and extends to the periphery; also that when a lower lobe is involved the costophrenic angle is obliterated and the process is usually though not always bilateral. Further, in bronchiectasis, cavitation is invariably present, with shadows suggesting dense fibrosis around the cavity. When bronchiectasis is suspected, the patient should be induced to attempt the evacuation of the contents of the cavity by forced coughing and expectoration, in order that the cavitation may be shown more clearly in the second roentgenogram.

Pulmonary abscess and encysted empyema are usually not difficult to differentiate from carcinoma. In such cases the areas of increased density are sharply circumscribed and surrounded by a shadow-zone of inflammatory change beyond which is the normal healthy lung area. The presence of the shadows of a fluid level with a gas-bubble above in an abscess cavity may be further aids. Finally, the shadow of a thickened pleura is more frequently associated with these conditions than with pulmonary malignancy.

In lobar pneumonia the shadows are usually localized, soft, and hazy,

and vary in density with the stage of the disease. In the early stage there may be only a slight difference in density from the surrounding lung tissue, while in the later stages the density is greater and the shadow is sometimes mottled. Any part of the lung may be involved, but the condition usually includes practically an entire lobe. The pleura is much more frequently involved. Clinically, of course, the differentiation is even more emphatic.

Regarding syphilis of the lung, very little is known definitely from the clinical standpoint and less from the roentgenologic standpoint. While the disease seems to be more common than formerly and is recognized clinically, Dr. W. W. Bissell informs us that he has never seen a case in 4000 postmortems. In one proved case in the Clinic the roentgen examination revealed marked enlargement of the mediastinal shadow, with areas of increased density in the regions of the main bronchi while the periphery was free. The heart shadow was greatly enlarged and the aorta dilated. At necropsy multiple diffuse areas of dense, patchy fibrous infiltration were found in both lungs near the hilus, together with a large heart showing marked myocardial changes and a saccular aneurysm of the ascending aorta. We have never seen, or at least have never diagnosed, gumma in the parenchyma of the lung. Gumma in the mediastinum may be differentiated from primary carcinoma of the lung. The shadow is usually large, well circumscribed, homogeneous, and unilateral or bulging to one side.

In primary sarcoma and lymphosarcoma of the lung the roentgenogram corresponds in its characteristics to that of mediastinal gumma, except that in sarcoma the tumor shadow tends to be larger. Infiltration and involvement of distant portions of the lung rarely occur.

In Hodgkin's disease the roentgenogram usually shows areas of increased density which are symmetric, bilateral, well circumscribed, and limited to the mediastinum. There are no changes in density along the course of the main bronchi unless the tumors are very massive or there is marked myocardial degeneration leading to much passive congestion.

In actinomycosis and allied affections of the lung the roentgen findings may be differentiated from those of primary malignancy. The areas of increased density are stringy and fan shaped in arrangement, usually found in the periphery, and surrounded by a soft shadow-zone of inflammatory reaction. The pleura is involved early and there may be an area of increased density corresponding to a tumor on the bony chest-wall.

There is a marked difference in the roentgen shadows found in primary and metastatic malignant disease of the lungs. As in the metastatic carcinomas, sarcomas, and mixed tumors, the roentgenogram shows the same characteristics, and their roentgen appearances may be enumerated collectively. According to Moore[3] and one of us (Carman), the areas of density in metastatic malignancy of the lung are rounded, regular, clearly circumscribed, soft, and homogeneous. They do not show a shadow-zone of inflammatory reaction surrounding them; they vary in size, are usually multiple, and may occur in any part of the lungs.

Cysts of the lung show in the roentgenogram as large, clearly circumscribed, and homogeneous areas of increased density. They are usually single and are found in the right lower lobe.

Fibromyxoma of the lung is easily differentiated from primary carcinoma. In the former the area of increased density is large, massive, homogeneous, and well circumscribed. An entire lobe is usually involved, most commonly the upper. Since the tumor is slow growing there is very little, if any, congestion shadow surrounding it.

The diagnosis from the roentgenogram of pulmonary tuberculosis will seldom be difficult. In chronic pulmonary tuberculosis the periphery is the common location of the areas of increased density, with very few, if any, changes in the hilus. The shadows are more circumscribed. The upper lobes, especially the apices, are usually the first and most commonly involved. Cavitation may be present, and there is frequently an associated pleuritis. In acute or subacute miliary tuberculosis the individual areas of increased density are smaller, more regular in shape, more discrete, more uniform in size, and with greater peripheral involvement than in the miliary type of carcinoma.

Pneumokoniosis produces symmetric "stringy" shadows distributed along and near the main bronchi; they never extend to the periphery. In the mediastinum enlarged calcified bronchial lymph-glands are present and show as clear-cut, rounded, and circumscribed areas of increased density.

Chronic passive congestion also produces symmetric stringy, diffuse shadows. In the hilus there are large, symmetric areas of increased density. The heart shadow is usually enlarged in both lateral directions, and fluid may be present.

In simple chronic pleuritis stereoscopic examination shows that the area of increased density is located on the surface of the lung. If lo-

cated at the base of the lung, the costophrenic angle may be obliterated and the areas of density limited by an oblique line.

In transudates and exudates into the pleural cavity the area of density is small or large, and homogeneous. It may present a fluid level that changes with position. Such conditions are usually located at the base and there is an obliteration of the costophrenic angle. The condition may be bilateral. The heart shadow may be enlarged, because of cardiac decompensation and dilatation, and the heart may be displaced.

Bronchoscopy is to be mentioned for completeness. It is a somewhat formidable procedure and usually impracticable except in the hands of the most expert, and even then it may be disappointing. Negative findings from the bronchoscopic examination should not be regarded as final. Exploratory thoracotomy should be considered in early, doubtful, and border-line cases, or when the patient's symptoms indicate the necessity of surgical interference.

The following are the histories of 5 cases of primary pulmonary carcinoma:

Case 176118.—A male, aged thirty-five years, a miner, registered in the Clinic October 24, 1916. The family history was negative for tuberculosis, cancer, and lues. The patient had had pneumonia thirteen years before, with the subsequent expectoration of one-half a teacup of purulent material supposedly from a small abscess in the right lung. Since then he had had good health. For the past eight months he had complained of a continuous dull ache in the right lower chest with some cough and expectoration. No fever or chills. Weight-loss, 16 pounds. Some dyspnea for years, but more marked in the past eight months and growing worse. Hemoptysis two months before, but only slight, probably 3 to 4 drams. No gastro-intestinal or urinary symptoms.

The physical examination showed considerable emaciation and some dyspnea on exertion. There were a large area of dulness, increased fremitus on exertion, and diminished breath-sounds below the angle of the right scapula. The systolic blood-pressure was 95; the diastolic, 72; the pulse, 76; and the temperature, 98.2 F. The urinalysis was negative. The sputum examinations were negative for tubercle bacilli. One blood Wassermann was negative.

In the roentgenogram could be seen a mottled area of increased density involving the lower right lobe and the base of the middle right lobe and extending outward along the bronchi though not to the periphery. The shadows were centrally placed; probably primary infiltrative carcinoma. There were multiple small areas of increased density, and in the lower left lobe, probably anthracosis (Fig. 288).

A clinical diagnosis was made of a probable chronic intrapulmonary lesion at the base of the right lung.

Operation: Exploratory thoracotomy. Three inches of the seventh and eighth ribs were resected on the right side in the posterior axillary line. The pleura was $\frac{1}{8}$ inch thick. The lung tissue was hard, tough, and coal-black, and for a finger's length had the same firm consistency throughout and bled easily. Specimens of the pleura and the lung were removed for microscopic diagnosis.

The pathologic diagnosis was primary pulmonary carcinoma.

CASE 159177.—A female, aged forty-seven years, registered at the Clinic May 8, 1916. The patient's father and one son died of tubercu-
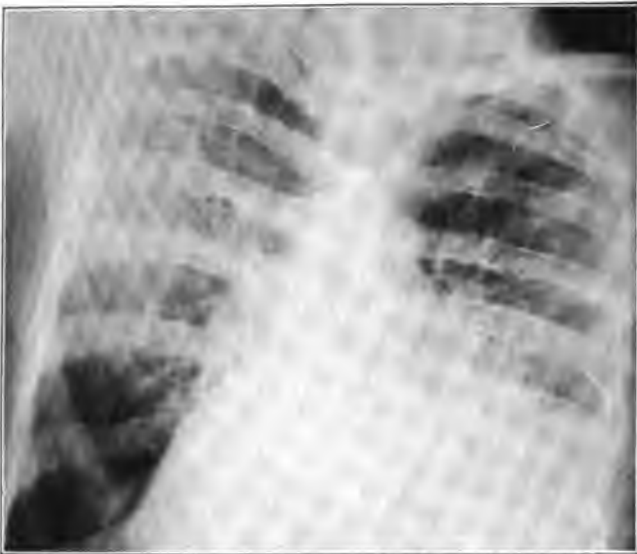
Fig. 288.

losis. One year previously she began to complain of weakness and dyspnea and was treated for hypertension. The loss of strength and the dyspnea had increased markedly during the past seven months and in addition she had a chronic irritative and non-productive cough. There had been no chills, fever, or sweats. She did not sleep well and had lost 25 pounds in weight in the past year. No pain; no gastro-intestinal, urinary, or cardiac symptoms.

The physical examination showed moderate emaciation and pallor. There were signs of moderate dulness at the bases of the lungs, crackling coarse râles, exaggerated breath sounds, and prolonged expiration. The average systolic blood-pressure was 140; the average diastolic, 98;

pulse-rate, 90; temperature normal. The vocal cords were negative. The urinalysis was negative. Hemoglobin, 83 per cent. Sputum negative for tubercle bacilli and carcinoma cells.

In the roentgen examination multiple diffuse areas of increased density were found throughout both lungs. The condition was believed to be primary carcinoma of the miliary type (Fig. 289).

The clinical diagnosis was primary carcinoma of the lungs.

Necropsy revealed primary carcinoma of the lungs with no evidence of metastases in the lymph-glands, liver, gastro-intestinal or genito-urinary organs, and no evidence of any other primary growth.
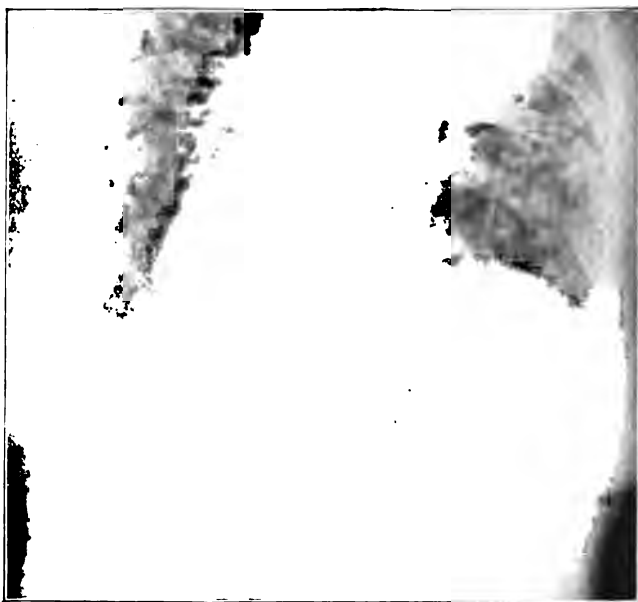
Fig. 289.

CASE 126018.—A female, aged seventy-one years, registered at the Clinic March 8, 1915. One brother had died of malignant disease. Patient's menstrual history negative; menopause thirty years previously. Complaint: Small, hard, painful multiple tumors in the left side of the neck which had been noticed ten months before for the first time. The nodules had gradually enlarged until three months previously. There was some pain down the left arm and soreness in the left shoulder. Considerable dyspnea was noted during this time. No choking sensations, dysphagia, or genito-urinary symptoms. No gastro-intestinal symptoms except slight loss of appetite during the past five or six months. The patient had lost 20 pounds in weight and considerable strength.

In the physical examination many enlarged, hard, tender glands

were found in the left cervical region. There were signs of multiple ill-defined areas of consolidation throughout both lungs. Urinalysis, Wassermann test, and sputum examination negative.

The roentgenogram showed multiple non-circumscribed areas of increased density throughout both lungs with equal distribution in the bases and the apices. Roentgen diagnosis, primary carcinoma of the mixed type (Fig. 290).

The clinical diagnosis was carcinoma of the lungs with metastases to the left cervical glands. The patient died at her home May 23, 1915. No necropsy.

Fig. 290.

CASE 109685.—A male, farmer, aged fifty-seven years, registered at the Clinic July 4, 1914. His family history and previous history were negative. He denied venereal infection. He had had dyspnea on slight exertion and loss of strength which had been increasing gradually over a period of four months. Slight cough; no expectoration, hemoptysis, night-sweats, or chills. His family physician wrote that his temperature had not been elevated and at times was subnormal. The patient complained of sleeplessness on account of cough, and of being unable to lie in a recumbent position. Up to the time of admission there was no history of edema or cardiac decompensation.

The physical examination showed the blood-pressure to be 118–78, pulse, 90; temperature, 98.2. The patient was well developed but slightly undernourished. His complexion was ashen, with cyanosis

exaggerated by slight muscular exertion. There were signs of consolidation in patches on both the anterior and posterior sides throughout both lungs, with numerous generalized, moist, crackling, and wheezing râles which, however, were more marked over the right lung. The heart-sounds were good; no murmurs. There was a slight mucopurulent discharge from the nares, more marked on the left side. Slight simple rhinitis and pharyngitis. Antra, negative. Urinalysis, negative. Hemoglobin, 86 per cent. White blood-cells, 9000. The sputum examinations were negative for tubercle bacilli and cancer cells.

The roentgen examination showed multiple areas of increased density throughout both lungs, with massive areas situated in the base of the
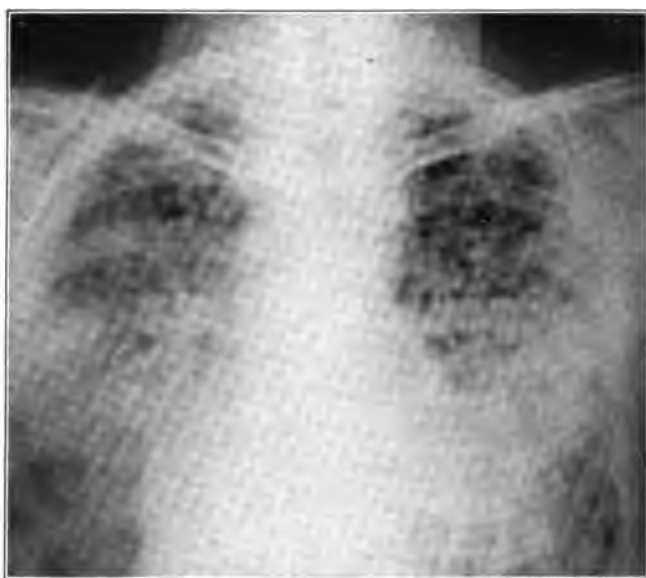
Fig. 291.

upper left and the middle right lobe. The roentgen diagnosis was primary carcinoma of the mixed type (Fig. 291).

The patient was treated symptomatically for eight weeks. The dyspnea increased and his strength diminished. During this time the myocardium showed marked decompensation. The pain in the chest was not pronounced. He developed symptoms of myocardial insufficiency, fluid in the chest, edema of the lower extremities, and the usual constitutional symptoms resulting from a chronic intoxication. Death occurred September 3, 1914, six months after the onset of the disease.

The clinical diagnosis was primary carcinoma of the lungs.

The necropsy (two months after the roentgen examination) revealed

400 c.c. of blood-stained fluid in the left pleural cavity.   The surfaces
of both lungs had an irregular nodular appearance and there were ex-
tensive chronic pleuritis and pleuropericarditis.   On section the lungs
showed multiple diffuse grayish-white nodules of regular and irregular
shape, varying in size up to 2 cm.   These were hard, resisted cutting,
and showed no tendency to central necrosis.   They were distributed
around the larger bronchi and bronchioles and in the lung parenchyma.
They were infiltrative rather than encapsulated and not sharply de-
lineated from the surrounding lung structures.   The lower half of the
upper right lobe and the base of the upper left lobe were almost com-
pletely occupied by hard massive tumors presenting on section the shape
of wedges with the apex pointing toward the hilus, to which they ap-
parently extended.   The bronchial and other lymph-glands were not in-

Fig. 292.

volved.   There were no evidences of tumor, either primary or second-
ary, in any other parts of the body (Fig. 292).

The final diagnosis was a mixed type of primary pulmonary carci-
noma, having its origin in the bronchial epithelium.

CASE 160751.—A male, aged sixty-one years, registered at the Clinic
May 26, 1916.   His mother died of carcinoma of the breast at sixty-
seven.   He had been married thirty years; his wife and two children
were living and well.   For the past six months he had had gradual loss of
weight and strength; with it, a slight hoarseness and change in voice;
no unilateral sweats.   During the same period of time he had had a dry
hacking cough; no hemoptysis.   He had noticed bluish discoloration
and distention of the superficial veins of the right forearm and hand.
There was no edema of the right hand and no pain.   A physician had

'17—44

stated that the right axillary gland was slightly enlarged and had advised dissection of the axillary glands for fear of malignancy. A partial excision of the right axillary lymphatics had been performed elsewhere in March, 1916, and the glands pronounced "not malignant." No gastrointestinal or genito-urinary symptoms. There had been a loss of 25 pounds in weight in six months.

The physical examination showed considerable emaciation and slight cyanosis of the lips and hands. In the right pectoral fold there was a recent operative scar of an incision that had healed by primary union. The larynx and cords were negative. Soft myocardial heart tones;

Fig. 293.

rhythm of beat regular; rate 100. There was moderate diffuse dulness throughout both lungs and poor expansion. The voice sounds were exaggerated. Prolonged expiration and crackling moist râles could be heard diffusely throughout the chest. The respiration was 26. The abdominal, genito-urinary, rectal, and urinary findings were negative. The hemoglobin was 76 per cent; white blood-cells, 10,800. The Wassermann test was negative. The sputum examination was negative for tubercle bacilli.

The roentgenogram showed multiple areas of increased density extending throughout both lungs with a massive area involving the base

of the upper right lobe.   The roentgen diagnosis was primary carcinoma of the mixed type (Fig. 293).

The clinical diagnosis was primary carcinoma of the lungs.

At necropsy, July, 1915, the examination of the thorax was limited. Both lungs and bronchial lymph-glands were found to be extensively involved with carcinoma.

Conclusions

1. There are three main types of primary carcinoma of the lungs which present characteristic gross pathologic appearances: The infiltrative, the miliary, and the mixed.

2. The roentgen examination and the stereoscopic study of roentgenograms will early point to a pulmonary lesion and its probable nature.

3. The areas of increased density found in primary pulmonary carcinoma are usually quite typical, and can be differentiated from areas of increased density caused by other diseases in the thorax, including inflammatory changes and neoplasms, both primary and metastatic.

4. A careful correlation of the roentgen findings with the clinical history and the physical and laboratory findings usually makes a clinical and differential diagnosis possible.

REFERENCES

1. Adler, I.: Primary malignant growths of the lungs and bronchi, a pathological and clinical study. London, Longmans, 1912.
2. Moore, A. B.: Roentgen diagnosis of bronchiectasis. Am. Jour. Roent., 1916, iii, 524–531.
3. Moore, A. B., and Carman, R. D.: Radiographic diagnosis of metastatic pulmonary malignancy, a report of seventy-one cases. Am. Jour. Roent., 1916, iii, 126–131.

THE RESECTION OF LOBES OF THE LUNG*

S. ROBINSON

Large portions of the lung may be removed from the normal animal with ease and without danger. This is by no means true in case of the sick man afflicted with chronic pulmonary disease. He is generally septic, his resistance is low, his bronchial tree is flooded with a profuse purulent secretion. He is moderately cyanotic. His blood color is low. The diseased lung lobes are firmly adherent to each other and to the diaphragm and the pericardium. The hilum of each lobe is inaccessible. The main lobe bronchus is generally thickened and diseased and unadapted to the technic of closure so successful in animals. The respiratory function and more particularly the circulatory mechanism are distinctly upset by operations for lung resection. The right heart labors in the early postoperative stage to adapt itself to the added demands on the pulmonary circulation. The sound lung labors to accomplish the work of two. This it cannot do when the embarrassed right ventricle fails to supply it with blood to be oxygenated. At best the convalescence following operation is both hectic and long. There is much suffering. The end-result may be only a partial cure. Later plastic operations are generally necessary to obliterate the pleural cavity and to repair bronchial leakage.

Let no man suppose, therefore, that removal of lobes of the lung is a trivial performance. Those of us who are pretentious enough to disclose our experiences in this regard do so more with apologies for our incompetence than with boasts of our success.

The indications for lobectomy are few, but these must be specific. Chronic, non-tuberculous lung abscess and bronchiectasis are at the present writing the only diseases to which such radical procedure should be applied, and then only in selected instances.

One lung must be absolutely sound. The disease must be confined

to one lobe, or at least one lobe and the adjacent portion of an adjoining lobe. There must be an absence of active tuberculosis. The heart must be a normal one. There must be complete absence of any systemic or organic disease. The individual should be under thirty-five years of age, certainly not over forty-five. There must be evidence that all non-operative methods have failed or are obviously bound to fail. There should be ample evidence that the existing pulmonary infection is not one that might be cured or relieved by direct drainage of the lung.

Given a young adult patient with chronic abscess or bronchiectasis confined to one or one and one-half lobes of one lung, whose resistance is not too low and in whom palliative treatment or drainage operations would obviously fail, lung resection may be considered. Nor should the patient be kept in ignorance of the dangers and discomfort associated with the procedure which you may propose to undertake. If all indications have been carefully studied and verified, the patient may properly be instructed that he may entertain no hope of cure without operation; that his existence will be a lingering and disgustingly offensive one both to himself and his associates; and that this existence will be of comparatively brief duration. Then it must be explained that the chances of relief or cure by the surgical alternative are between 60 and 70 per cent. If when thus informed the patient decides, after due consideration, to undergo operation, lung resection is justifiable.

I have employed a different technic in lung resection from that which we have all adopted in animals, and different from that employed in man by other surgeons. It consists in a several-stage operation with a multiple rib-resection exposure rather than a single operation with a wide intercostal exposure. I have argued that the division into stages reduces the insult to the respiratory and circulatory systems; that the intrapleural pressure is more gradually altered and the pulmonary circulation less suddenly overworked in the several-stage rib-resection method than in the single operation through an intercostal opening. I have been of the opinion that while these disturbances are equally well cared for during operation, the dangers associated with them in the first twenty-four hours after operation by the one-stage method are obviated by the several-stage operation.

FIRST STAGE

Neither differential pressure nor intratracheal insufflation has been used in this series, nor has their omission been regretted. The incision

is crescentic, with its convexity downward, starting at the fifth rib, two inches from the vertebral column, crossing the eighth rib in the scapular line, and terminating at the level of the sixth rib in the mammary line.

The skin and fat are dissected upward from the muscle for an inch. Vessels are clamped and tied. The latissimus muscle-fibers are separated vertically to admit long-bladed curved muscle clamps, which are applied in series above and below in the direction of the sternum and again toward the vertebral end of the wound. The muscle-fibers are then divided transversely between the clamps.

The field thus exposed should permit the subperiosteal resection of the seventh, eighth, and ninth ribs from their angles to the anterior axillary line. The intercostal bundles are then ligated and removed. The skin and muscle-flap is then replaced. The wound is closed tight. The thoracic window has been made ready to open. The chest-wall collapse necessary for the subsequent obliteration of the space left after amputation of the lower lobe is provided. Something has been learned of the individual's resistance to surgical trauma, and of his tolerance of anesthesia.

SECOND STAGE

The interval prior to the second stage should be approximately a week in length. The power of expelling sputum should have been restored; all trace of shock should have disappeared; and the temperature should approach "normal."

The skin stitches are removed, the scapula and flaps retracted, and the pleura again inspected. It will be found that in the upper part of the exposed field there are new pleural adhesions anchoring the upper lobe. The lower lobe is still adherent at various places, now somewhat retracted and purple red in color. The pleura is opened wide at any point, whether adherent or not. There will·be no particular change in respiration or pulse.

The separating of adhesions necessary to deliver the lower lobe is generally irksome. It is the difficult part of the operation. The lower lobe is generally bound to the diaphragm and costodiaphragmatic angle by tough, unyielding bands which may not yield under digital pressure. If undue force is used in stripping, the lung surface will tear before the adhesion gives way. Some of these should be cut. It is well, therefore, to free the lobe first from all except its diaphragmatic attachments, so that if bleeding occurs during the separation of the latter a clamp may be

applied temporarily in the region of the lobe hilum. The interlobar fissure does not always provide a simple cleavage, nor is it advisable to employ too much force in this region lest the light adhesions be parted which by now should be holding the upper or middle lobes to the parietes. The pericardial surface is least troublesome of all.

To stop the operation at the middle of the second stage and to defer the completion of adhesion-stripping and the amputation to a third stage is a conservative measure not to be regretted, and one which in difficult cases may save the patient from undue hemorrhage, shock, and carbon dioxid poisoning.

AMPUTATION

If there has been no occasion to close the second stage prior to the complete delivery of the lower lobe, amputation is promptly performed as follows: A long curved clamp is applied to the root and closed to the last notch. The lobe is then amputated at least a half-inch distal to the clamp. The veins, arteries, and bronchi are then picked up separately and ligated with No. 2 chromic catgut. A mass ligature of kangaroo tendon or braided silk is then placed just proximal to the clamp and tied as the clamp is slowly released, the ligature being guided into the crushed area evacuated by the clamp. Not infrequently two clamps are necessary safely to include the whole stump. It is apparently an equally satisfactory method to leave the root clamps in situ and to remove them on the seventh day.

Both of these methods of amputation result invariably in subsequent leakage of the bronchial stump. The portion distal to the mass ligature or clamps sloughs away within a week or ten days, leaving one, two, or three fistulous openings of small caliber. Experience will prove whether or not it is expedient to attempt any special technic for hermetically closing the bronchus at the time of amputation. The bronchus at the point of division is generally dilated; its walls are thick, tough, and unyielding. It is probably not amenable to such treatment as invagination and end-suturing, which has been successful in normal animals. If treatment of this kind were attempted, it would necessitate the isolation of the bronchus from the vessels in the hilum, the individual double ligation of the vessels before their division, and the crushing, division, cauterization, invagination, and suturing of the bronchus. Neither the clamp nor mass ligation could be employed. In the present period of undeveloped surgery of the diseased lung it would seem more proper not to sacrifice time at the end of a critical operation by any finesse in the

treatment of the bronchial stump, which in its pathologic condition would stubbornly resist any technic of closure.

The minute fistulas consequent on the clamp and mass ligature technic in no way complicate the convalescence. The pleural space is rapidly obliterated, the fistulas remaining the only unhealed points in the wound. By local plastic surgery under local anesthesia the fistulas are closed later by the superimposing of a skin-and-fat flap.

The after-treatment of the second operation is simple. Bronchial secretion is no longer a cause for anxiety. Within the first two days the bronchial tree becomes free from the residue emptied into it from the lower lobe just previous to its removal.

With return of consciousness the patient discovers that the promised reward of his long siege of treatment is now a reality. The sudden freedom from a cough of perhaps ten years' duration is a stimulus mentally and a boon physically.

The pack is not disturbed for four days, by which time it is foul. At least two-thirds of it can then be removed painlessly. When firmly adherent to the raw surfaces of the parietal pleura, fragments of the gauze should be left till they have sloughed away. Again, precaution is taken at each dressing to repack the persisting pleural space completely lest pocketing occur in the costodiaphragmatic angle or about the pericardium or posteriorly below the lower limits of the neighboring lobe. At no time in the convalescence should drainage-tubes be substituted for gauze. The skin opening has been so designed that it will not close until the cavity is obliterated. Irrigation is never indicated. Granulations may be stimulated with balsam of Peru. The pleural space remaining after excision of the lower lobe, having been already diminished by the shrinkage of fibrosis attendant on the first two stages, may now be obliterated within four months. The patient meanwhile attains a body weight equal to his previous maximum, and this continues to increase rapidly during the months following closure of the wound.

TUBERCULOUS ABSCESS OF THE THORACIC WALL*

S. ROBINSON

Dispensary clinics are not infrequently visited by patients present-ing on the anterior or lateral aspect of the chest an indolent discharging sign. The absence of accompanying symptoms doubtless explains the patient's characteristic lack of concern. He related the discovery, at some previous moment, of a hard, deep-seated swelling upon his chest, neither painful nor tender, which has gradually come to the surface, softened, and broken, discharging a watery pus which continued un-abated. The out-patient surgeon is as prompt in recognizing and nam-ing such lesions as he is ignorant of their pathology. "Necrosis of a rib," "caries of the rib," "T. B. of the chest-wall," "cold abscess," "tuberculous ribs," are the common diagnostic terms. Tradition and school text-book teaching have pigeon-holed such lesions in the diagnos-tician's cerebrum under the label "sick ribs," whereupon he promptly refers the afflicted to a surgeon, with the presumption, rarely unwar-ranted, that a rib will be either scraped or excised. To complete the deception, the roentgenologist, seeing the skin lesion responds to the dictates of tradition, appreciates that it is incumbent upon him to show the sick rib—and also, too often, seems to see what may exist only in his imagination and not on the plate.

The inevitable operation, generally classified as too trivial and un-interesting to require particular skill, falls to an assistant surgeon or intern. He may dilate the sinus and curet, scraping the adjacent rib until it feels necrotic, though perhaps not so in reality. If more per-severing, he may enlarge the wound and resect a fragment of rib to which the fistulous tract may appear to lead. If the resected rib is grossly normal, the pathologist hopefully examines and decalcifies, generally finding some minute excuse for a report of rib necrosis.

I have related this instance of hospital departmental coöperation which so often perpetuates a medical fallacy until the discovery of the true pathology of the lesion reminds each department that it need not strain its imagination to find what may not be present. That a sinus of the chest-wall may lead to a primary tuberculous lesion of the rib is undeniable. That the removal of a piece of normal rib, by exposing an underlying abscess cavity, may be of therapeutic value, is also true.

The purpose of this paper, however, is to demonstrate that a cold abscess of the chest-wall may exist without any involvement of the rib[2]; that an erosion or necrosis of the rib may be merely incidental to a primary lesion of the pleura, and that its removal as such may be inadequate treatment of the lesion[3]; that excision of rib should be employed not as the sine qua non of the operative treatment, but as an incidental step in the scrutinous exploration of the fistulous tract and in the wide-open drainage of the subcostal abscess cavities with which the tract generally communicates.

The discussion of the etiology of cold abscess of the chest-wall is contributed chiefly by French writers. Until 1865 caries of the rib had been universally regarded as the cause. Then appeared Leplat's exhaustive thesis, expounding a theory with ample proofs that tuberculous disease of the pleura or of the lung is not infrequently the source of these abscesses. He writes: "Inflammations of the pleura, instead of limiting themselves to the tissue primarily invaded, involve also the surrounding tissue and are causes in certain instances of abscesses of the thoracic walls."

Gaujot, at Val-de-Grace, presented a theory describing an external periostitis. Duplay, in 1876, inclined to the views of Gaujot, in a clinical lecture distinguished three varieties of cold abscess—one of the cellular tissue, one from the periosteum, a third of deep origin in the bone. He describes these abscesses as in front of the ribs, behind the ribs, and of the shirt-stud variety, in which a superficial and deep abscess communicate through an intercostal space. The etiology described by Gaujot was accepted for almost twenty years, in which time Verneuil, Charvot, Peyrot, Poulet and Bousquet, Tuffier, and Bonnaud, with slight differences in opinion, supported the periosteal and osseous theory.

In 1894 Souligoux again takes up the banner of Leplat, placing the pleuropulmonary theory definitely among the chief etiologic factors of chest-wall abscess. Peron, Villar, Paget, and Poirier have since con-

tributed case reports which definitely support the pleuropulmonary theory.

REFERENCES

1. Bonnaud: Abces froids des parois thoraciques. Thèse de Paris, 1892, No. 173, 50 p.
2. Bousquet: Abces froids des parois thoraciques consecutifs aux periostites externes chroniques. Arch. gén. de méd., 1878, 7. s., i, 288–313.
3. Charvot: De la periostitie externe chronique. Gaz. hebd. de méd., 1879, 2. s., xvi, 630–635. Quoted by Souligoux, loc. cit.
4. Duplay: Abces chroniques des parois thoraciques. Prog. méd., 1876, p. 489. Quoted by Souligoux, loc. cit.
5. Gaujot: Leçons cliniques faites au Val-de-Grace. Quoted by Souligoux, loc. cit.
6. Leplat, E.: Des abces de voisinage dans la pleuresie. Pathogenie et étude clinique des abces parois thoraciques. Par., Asselin, 1865, 50 pp. Also, Arch. gén. de méd., Par., 1865, 6 s., v, 403 and 565.
7. Paget, S.: Cited by Vadon, loc. cit.
8. Peron: Recherches anatomiques et experimentales sur les tuberculoses de la plevre. Thèse de Paris, 1895–96.
9. Peyrot: Le thorax des pleuretiques et la pleurotomie. Thèse de Paris, 1876. Quoted by Souligoux, loc. cit.
10. Poirier: Quoted by Souligoux, loc. cit.
11. Poulet: Quoted by Souligoux, loc. cit.
12. Souligoux, C.: Pathogenie des abces froids du thorax. Par., Steinheil, 1894, 154 pp. Thèse de Paris.
13. Tuffier: Des abces froids des parois thoraciques (mediastinitis tuberculeuses). Semaine méd., 1890, x, 385. Quoted by Souligoux, l. c.
14. Vadon, A. M.: De l'origine pleuro-pulmonaire des abces froids thoraciques et de leur traitement. Bordeaux, Gassignol, 1905, 79 pp., p. 15.
15. Verneuil: Prog. méd., July 15, 1876. Quoted by Souligoux, loc. cit.
16. Villar: Gaz. hebd. d. sc. med. de Bordeaux, December, 1904.

RECURRENT OR HABITUAL DISLOCATION OF THE SHOULDER*

M. S. HENDERSON

Dislocations occur more frequently in the shoulder-joint than in any other joint in the body. Reduction is, as a rule, readily accomplished, but if delayed beyond a few hours, is not easy. If deferred for days, it is quite difficult, and a delay of more than a week may mean that all attempts at reduction will fail. If the dislocation is associated with a fracture of the surgical neck of the humerus, unless reduction is accomplished by an open operation, the patient usually comes to a resection of the head of the bone later.

Habitual dislocations of the shoulder-joint occur in cases in which reduction having been accomplished and the convalescence completed without incident there has been no cause for anxiety. The habit of easy dislocation is a sequela that cannot be foretold. A shoulder-joint may be said to be subject to habitual or recurrent dislocations when they occur irregularly as the result of some trivial voluntary manipulation or effort on the part of the patient.

The shoulder-joint is a true ball-and-socket joint. The depth of the socket is so slight and the amount of the head of the bone in actual contact with the glenoid fossa so small that it is a wonder dislocations of the shoulder are not much more common. The socket is formed by the glenoid fossa of the scapula and its cartilaginous rim. The capsule itself is quite lax, the shoulder owing its stability to the muscular arrangement. It is reinforced at certain points by the insertion of muscles into and through it, to the bone beneath. When the shoulder-girdle is paralyzed and the muscle-tone gone, as in anterior poliomyelitis, or trauma to the brachial plexus, we see the lax dislocated shoulder which cannot be kept in place. The long head of the biceps originates from the upper margin of the glenoid fossa, and crosses the cavity of the shoulder-joint
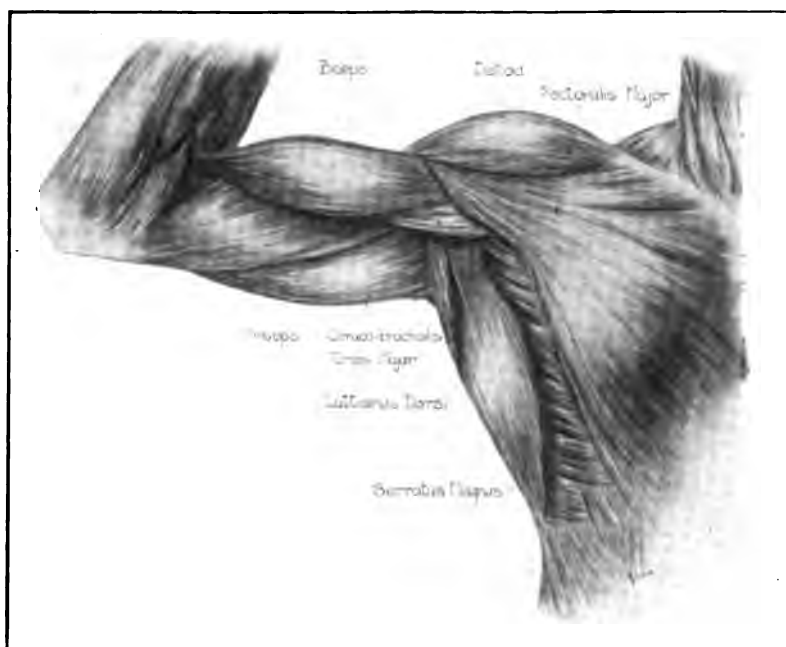
Fig. 294.—Anterior view, showing muscular arrangement about the shoulder.

Fig. 295.—Posterior view of shoulder, showing insertion of supraspinatus, infraspinatus, and teres minor muscles.

anteriorly, surrounded by synovium (Fig. 294). Its action in this situation serves to strengthen the joint and prevent dislocations through this part of the capsule. Over the whole is the strong, fan-shaped deltoid, which by its action tends to hold the head of the humerus in the glenoid fossa. The supraspinatus, infraspinatus, and teres minor inserted into the greater tuberosity of the humerus thicken and strengthen
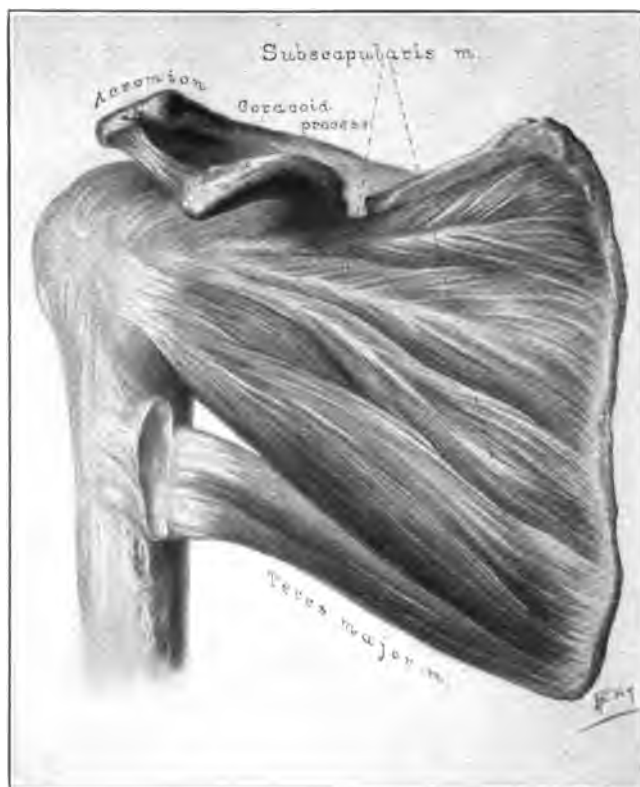
Fig. 296.—Anterior view of scapula, showing insertion of subscapularis and teres major muscles.

the capsule above and behind, and by their action tend to hold the head of the humerus in place (Fig. 295). Into the lesser tuberosity of the humerus the subscapularis tendon is inserted in front and into the inner side of the bicipital groove, serving to strengthen the anterior part of the capsule (Fig. 296). At the lower margin of the glenoid fossa arises a part of the triceps in no way reinforcing the capsule, and between this point below and the point of insertion of the subscapularis above there

is no muscular insertion on the anterior portion of the capsule.   This area is the weak part of the capsule, being the place in which dislocations usually occur (Fig. 297).

Definite evidence of the pathologic condition is lacking.   The limited opportunity for examination of the entire field at the time of operation accounts for much of the difference of opinion.   In 1880 Joessel gave it as his opinion that the dislocation was the result of a tear in the capsule at the attachment of the supraspinatus and infraspinatus and the teres minor.   Such a rent, he contended, would allow the arm to drop down
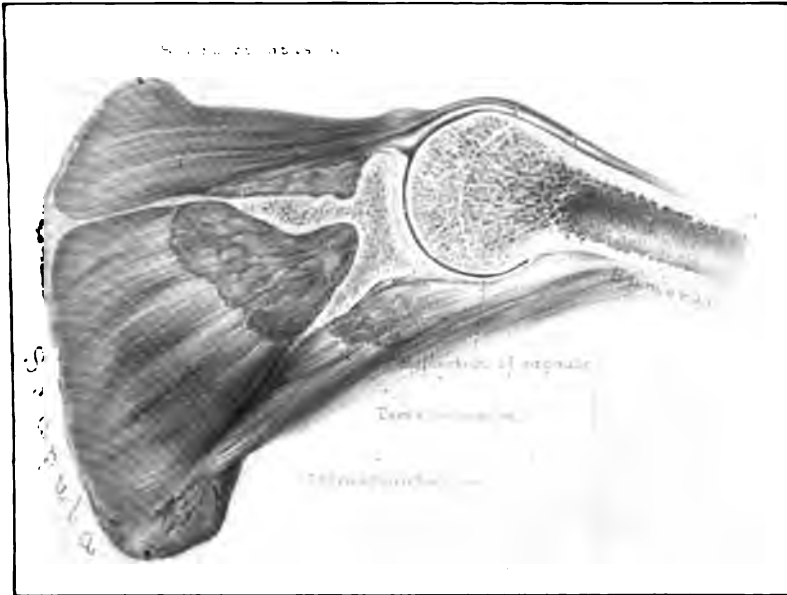
Fig. 297.—Frontal section through right shoulder-joint, viewed from behind.

and luxate through the lax portion of the capsule between the insertion of the supscapularis above and the origin of the triceps below, without necessarily tearing this lax portion.   Thomas does not agree with this view, asserting that in his opinion the rent usually occurs in the anterior inferior portion and that there is no damage to the capsule in the region of the greater tuberosity.   In none of the cases in this series has there been any evidence of rupture of the supraspinatus and infraspinatus tendons and damage to the capsule.   It might be supposed that a rupture of these tendons would tend to detach some of the periosteal cells

from the greater tuberosity, and that the callus thus formed would cast shadows on the plate, but the roentgenograms in every case in this series were negative.   Also the curative value of a capsulorrhaphy of the anterior inferior portion of the capsule would further substantiate the theory that this is the point of exit for the dislocating head.   Other authorities, such as Loebker, suggest some abnormality or defect in the head of the humerus, but their proof for such a condition is not very convincing.

There is always a history of a traumatic dislocation.   The second dislocation may occur a few weeks or a few months after the first, and those that follow gradually become more frequent.   The motion-producing luxation is one with the arm in abduction and a little forward. The position causes the greater part of the humeral head to be pressed against the weak part of the capsule and at the same time relaxes the biceps tendon as it runs in the bicipital groove.   The dislocations may occur so often that the patient, or his friends under his direction, may make the reduction.   The number of dislocations and the degree of disability vary in individual cases.   One patient in the series had had more than a hundred dislocations.   As would be expected, dislocations are more common in the male than in the female, the proportion in this group being seven males to one female.   They are found in the young and middle-aged, and are by no means unknown in the aged.   Epileptics are subject to the disability.   The disability due to the uncertainty and irregularity of the attacks may be so extreme that the patients are unable to earn a livelihood.   It is generally stated that recurring dislocations are caused by insufficient fixation following the original luxation.   This is probably true, but the fact remains that when the ordinary dislocation is reduced and the patient is allowed to go about his usual duties in a few days, subsequent dislocations rarely occur. To safeguard our patients against this disagreeable sequela, the arm should be carried in a sling for ten days and abduction of the shoulder absolutely prohibited for one month following the accident.

As braces and appliances are cumbersome and seldom successful in the treatment, there remain only surgical measures.   In the past, extreme measures have been undertaken to relieve the condition.

Resection of the head of the humerus has been done by some surgeons, notably Cramer, Kuester, Kraske, Popke, Volkmann, Schueller, Staffer, Mueller, and Francke.   Such a procedure is mentioned only to be condemned.   Albert prevented the recurrences in his cases by pro-

ducing a bony ankylosis, and while this seems somewhat extreme, it might readily be advised if milder measures failed.   An ankylosis of the shoulder-joint produced with the humerus at a right angle to the body gives a very useful arm, as has been shown in cases of infantile paralysis in which such operation has been performed because of paralysis of the deltoid.   The scapular vertebral muscles acting on the scapula are used to abduct the arm.   It has been found that by merely incising the capsule at the anterior inferior angle and overlapping it, by the process of capsulorrhaphy, the dislocations are prevented.   Gerster in 1883 was
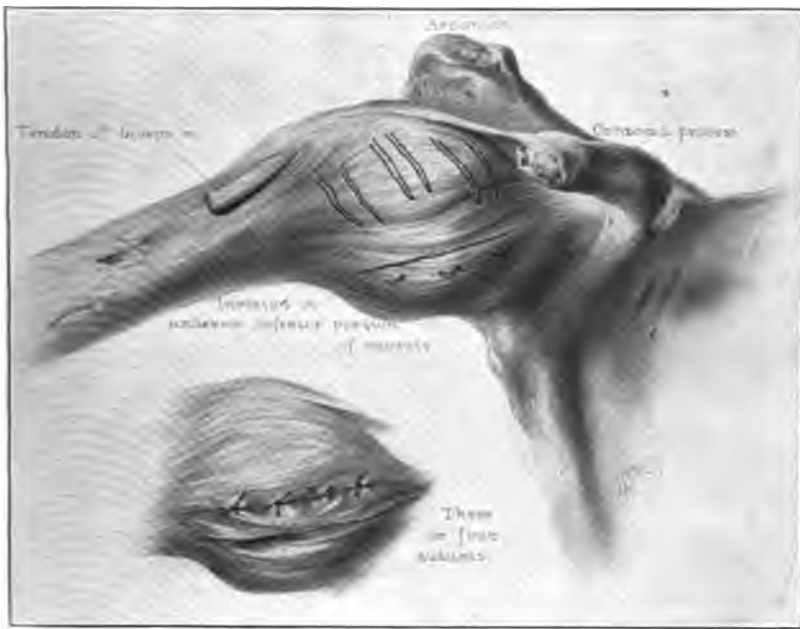
Fig. 298.—Capsule, showing overlapping (capsulorrhaphy), with four doubled chromic catgut sutures in place.

the first to do this.   Bardenheuer did the same in 1886, and Ricard in 1892.   More recently Thomas has reported cases in which cure has been effected by capsulorrhaphy.   Young has outlined a method, basing his operation on the fulcrum action of the pectoralis major and the latissimus dorsi.   The operation consists in the severing of the lower portions of these muscles at the point at which they are inserted into the lips of the bicipital groove.

To expose the capsule of the joint for capsulorrhaphy, an incision is

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made which runs along the anterior fold of the axilla while the arm is held in abduction. The pectoralis major muscle is strongly retracted and the dissection is carried down onto the capsule below the tendon of the subscapularis. An incision is made into the capsule and three or four mattress sutures of No. 2 chromic catgut doubled are inserted (Fig. 298). It will be found that the overlapping of the capsule may be secured readily by rotating the arm. The sutures are placed in the weak, lax part of the capsule at the inferior anterior portion. The wound is closed, the arm is held strapped to the side of the body for two weeks, and abduction to a right angle is not permitted for six weeks.

The plastic operation of Young is accomplished by an incision which starts a little farther out on the axillary fold and extends a little farther down onto the humerus over the bicipital groove. The tendon of the pectoralis major is brought into view and the lower half severed. The latissimus dorsi on the opposite side of the biceps tendon is exposed and the inferior part of this is divided. The arm is then placed in a plaster-of-Paris spica, and is held at a right angle to the body for from ten days to two weeks.

The question confronting the surgeon is which operation to choose in order to secure the relief desired. From a study of this group of only eight cases I am unable to answer the question. The principles underlying the operations are dissimilar, and I know of no way of determining beforehand which procedure offers the best chance for cure. It is possible that if the capsule is strengthened, it will withstand the fulcrum action claimed by Young. On the other hand, the weakened capsule may withstand attempts at dislocation if the fulcrum is weakened, if the operator will lengthen part of the tendons of the pectoralis major and the latissimus dorsi.

Eight patients (7 males and 1 female) have been operated on in the Mayo Clinic for recurrent dislocation of the shoulder-joint. One operation, performed July, 1917, is too recent to report, although the patient is well at the time of writing (October, 1917). Five of the remaining 7 may be called cured. There is one in whom the operation is a failure, though really only a partial failure, for whereas previous to the operation he had 12 or more dislocations a year, in the last year and a half he has had only 2. In one other case the treatment is apparently a distinct failure after both a capsulorrhaphy and a lengthening of the tendons of the latissimus dorsi and the pectoralis major. If the patient in this case

returns, I shall advise an arthrodesis of the head of the humerus and the glenoid fossa with the arm at a right angle.

REPORT OF CASES

CASE 66183.—W. C., a man, laborer, aged twenty-four years, came to the Clinic for examination April, 1912.   Six years previously he had dislocated his shoulder and the dislocation had not been reduced for thirty-six hours.   After that there had been multiple dislocations, not prevented by apparatus.   Capsulorrhaphy was performed April, 1912, and there were no dislocations until November, 1913.   January, 1914, the Young operation was performed.   The man has since had dislocations and the case must be called a failure.

CASE 87419.—H. W., a man, laborer, aged twenty-five years, came for examination July, 1913.   Five years before his left shoulder had been dislocated in a runaway accident.   Later he had had seven dislocations, and was incapacitated for a month after each.   There had been an interval of two years between the last two dislocations, the latest one occurring June, 1913.   Capsulorrhaphy was performed July, 1913, and in a communication from the patient August, 1917, he said he had had no further trouble and was doing everything he wished to do with his arm. The case may be classified as a cure.

CASE 90312.—L. L., a man, clerk, aged nineteen years, was first examined August, 1913.   Eighteen months previously the shoulder had been dislocated while he was playing hockey.   During the eighteen months the dislocation occurred probably a dozen times, the last time while he was swimming.   Capsulorrhaphy was performed August, 1913, and in a communication from his mother, September, 1917, it was stated that the arm feels somewhat weak but that no dislocations have occurred.   The case may be called a cure.

CASE 107485.—M. G., a man, merchant, aged forty-one years, was examined June, 1914.   Nineteen years before he had fallen and dislocated his right shoulder.   It was reduced immediately.   There were several dislocations during the next four years, and then he caught a cold which seemed to settle in the right shoulder.   For four months there was a soreness which prevented his lifting the right arm to the head. After that he had numerous dislocations, and ten years prior to the examination he fell, and in catching himself, dislocated the left shoulder. The left shoulder has not been dislocated, however, for two years, and we consider the dislocation merely the result of an ordinary trauma. The right shoulder, however, had been out of joint repeatedly, the last dislocation being three weeks before the examination.   Capsulorrhaphy was performed June, 1914, and in a communication August, 1917, the

patient asserts that he has had no further trouble, and that he gets along very nicely.

CASE 118613.—R. V. A., a man, bookkeeper, aged thirty-three years, was examined November, 1914. After a dislocation of the left shoulder seven years previously he had had recurring dislocations—at least twelve a year. He sometimes threw the shoulder out of joint in reaching for a book or anything on a shelf. November, 1914, capsulorrhaphy was performed. The patient was not troubled until May, 1915, when he had a peculiar feeling that his shoulder was going to slip out. He now reports that during the last year—two and one-half years after operation—the shoulder has slipped out twice. This case should not be put down as a distinct failure, since the shoulder is really improved and the function is markedly improved. As the patient intends to return for observation, I have recommended that the Young operation be performed to see if it will stop the trouble.

CASE 123803.—S. F. L., a man, lawyer, aged twenty-five years, was examined February, 1915. Eight years previously he had dislocated his shoulder playing football. The next time it was dislocated while he was swimming, the third time while he was playing baseball, and it had even slipped out while he was sleeping. At the time of the examination he was wearing a band around the body to hold the arm to his side. He had worn this steadily for a year and a half, thus averting dislocations. The condition had completely incapacitated him for any participation in athletics. Capsulorrhaphy was performed February, 1915, and in a letter from him dated August, 1917, from an officers' training camp, he says he has been able to do his bit in such strenuous tests as digging trenches, bayonet exercises, and trench storming, without suffering the slightest inconvenience or trouble from the shoulder.

CASE 156847.—J. C. S., a man, merchant, aged thirty years, was examined April, 1916. Ten years before he had dislocated his shoulder. The dislocation remained for two days, and then reduced itself, which would lead one to believe it must have been a subglenoid dislocation. The shoulder has been dislocated many times since, and he has had to take gas, ether, or chloroform about ten times. April, 1916, the Young operation was performed. In a letter dated August, 1917, he states that he has had no further trouble and that this shoulder seems to be as strong as the other.

CASE 200995.—H. J., a woman, nurse, aged thirty-three years, was examined July, 1917. On Thanksgiving day, 1915, she fell and dislocated her shoulder. It was reduced about an hour later, and was held to the side for ten days. The next dislocation occurred Christmas day, 1916, to be followed by four dislocations. Capsulorrhaphy was performed

July, 1917, and up to the time of writing, October, 1917, there have been no further dislocations.

CONCLUSIONS

1. Recurrent dislocations of the shoulder may be cured by operation, capsulorrhaphy being the operation of choice.

2. Capsulorrhaphy has been found to be sufficient in the majority of cases.

3. Resection of the head of the humerus is not permissible for the condition.

4. Arthrodesis or ankylosing of the head of the bone to the scapula with the arm at a right angle would be an extreme measure, but permissible.

REFERENCES

1. Albert, E.: Arthrodese bei einer habituellen Luxation des Schultergelenkes. Internat. klin. Rundschau, Wien, 1888, ii, 281–283.
2. Gerster, A. G.: Fracture of the humerus and scapula, complicated with severe injury of the entire brachial plexus, followed by paralysis. Med. News, Phila., 1884, xliv, 421.
3. Joessel, J. G.: Ueber die Recidive der Humerusluxationen. Deutsch. Ztschr. f. Chir., 1880, xiii, 167–184.
4. Thomas, T. T.: Habitual or recurrent anterior dislocation of the shoulder. I. Etiology and pathology. Am. Jour. Med. Sc., 1909, cxxxvii, 229–246; II. Treatment. Ibid., 267–377.

DIAGNOSIS AND TREATMENT OF TUBERCULOUS ARTHRITIS OF THE HIP-JOINT*

H. W. MEYERDING

Shortening and ankylosis in deformity, after prolonged suffering and disability, are the results of nature's cure of tuberculous disease of the hip. Abscess-formation with annoying multiple sinuses frequently complicates the condition and adds to the misery of the patient. To avoid these end-results, early diagnosis and careful, prolonged treatment must be carried out under competent supervision.

While tuberculous disease of the hip is usually found in the first decade, Whitman's[1] report of 88.1 per cent of patients under ten, and 45.6 per cent between three and five years of age, and a review of cases observed at the Mayo Clinic, leads us to conclude that our practice consists principally of long-standing, severe, or neglected cases. In 100 consecutive cases there were 23 patients in the first decade, 23 in the second, 24 in the third, 22 in the fourth, 4 in the fifth, and 4 in the sixth. The average duration of the disease before our examination was twenty months, the earliest two weeks, and the most prolonged, forty-six years. The histories clearly show early diagnosis and that proper treatment was instituted, only to be discarded at the termination of acute symptoms, to be followed by recurrence, the formation of abscess, ankylosis, etc. Fifty-six per cent of these patients were males and 44 per cent females. The right hip was affected in 60 per cent.

A diagnosis should not be made by roentgenograph alone, nor should it depend entirely on laboratory findings, but rather on a carefully written history, a clinical examination substantiated by the roentgenograph and the laboratory findings. The fact that Perthe's osteochondritis deformans juvenilis has been but recently differentiated from tuberculous arthritis makes this summarization of findings in diagnosis obvious. The history is of great importance in bringing out the insidious onset, the exposure to trauma and infection, etc.

* Presented before the Southern Minnesota Medical Association, Mankato, Nov. 26-27, 1917. Reprinted from Minnesota Medicine, 1918.

Forty-four per cent of our patients gave a history of trauma directly preceding the primary complaint, and referred to it voluntarily as the cause of the arthritis.   Trauma was the most frequent cause of remission of symptoms, those second in importance being illness or pregnancy. Exposure to tuberculosis in the home was noted in 17 per cent.

Among the earliest symptoms are muscle-spasm, limping, pain, and atrophy.   The patient frequently rests the well foot on the affected one, and pushes down in the effort of traction and fixation.   Pain is often referred to the knee-joint.   Night starts and cries may or may not occur and are not in themselves diagnostic, but associated with other symptoms, aid in the conclusions.   Later, deformity, shortening, periarticular thickening, and cold abscess-formation may become evident.

Roentgenographic findings are dependent on the stage of the disease, varying from synovitis, and thickened or distended capsule, to areas of rarefaction and general haziness or destruction of the entire joint and acetabulum, with upward displacement of the greater trochanter.   Even perforation of the acetabulum and sequestrum in the urinary bladder may occur.   In our series there were two cases of perforation of the bladder.   One patient was operated on, the sequestrum proving to be the femoral head.

Von Pirquet's test is of the greatest value as an aid to early diagnosis in children under two years of age.   Its value decreases with increasing age.   Aspiration and guinea-pig inoculation, proving the presence of tubercle bacilli, are final evidence.   Our observations would lead us to believe that there is, independent of Perthe's disease, a mild and fulminating type of tuberculous arthritis.   The blood count is of value as showing increase in lymphocytes and secondary anemia.   In 48 patients the hemoglobin averaged 67 per cent.   The temperature, night-sweats, other tuberculous lesions, etc., give further evidence of the disease.

DIFFERENTIAL DIAGNOSIS

1. Traumatic arthritis or periarticular injury is easily differentiated by local tenderness, ecchymosis, the history, and a negative roentgenograph, while impaction-factures, later causing a limp, and shortening due to loosening up of the impaction, give positive roentgenographs.

2. Chronic hypertrophic arthritis has frequently been confused with the tubercular arthritis.   The condition appears in older persons, and shows characteristic lipping arthritis without rarefaction, etc.   The limitation of motion is usually in abduction and rotation due to me-

chanical obstruction and there is little or no muscle-spasm, shortening, etc.

3. Infectious arthritis is usually multiple, acute, and accompanied by high fever and leukocytosis. A search for focal infection and its removal lead to rapid recovery. Aspiration and bacteriologic examination aid in differentiation. The observation of the patient may be necessary for some time.

4. Perthe's disease, osteochondritis deformans juvenilis, may resemble tuberculosis clinically, but may be differentiated by the characteristic epiphyseal changes.

5. Infantile paralysis is easily differentiated in the paralytic stage. In the acute stage there may be local pain and tenderness for a short time, which soon leave a typical paralysis.

6. Arthritis of the knee allows motion of the hip without pain when the knee is held immobilized, and the entire limb carefully manipulated. An examination of the hip should always be made when pain in the knee is complained of without local objective findings.

7. Pott's disease of the lumbar spine has as its earliest symptom muscle-rigidity. Careful manipulation of the hip with negative roentgenographs will make clear that the hip itself is not involved.

8. Congenital dislocation lacks muscle-spasm, rigidity, atrophy, etc., and is positively diagnosed by the gait, palpation, and the roentgenograph.

TREATMENT

The general hygienic antituberculous care of the patient is of the utmost importance. Rollier's[2] methods are productive of excellent results. Sunshine, fresh air, and simple substantial food are the most useful general aids, and preferable to dosing the patient with medicine, although tonics and constructives have a value. The use of a sun porch is urged, and patients are instructed to live thereon. They should sleep with windows open, and be properly protected against wind and cold.

The local treatment is dependent on the stage of the disease and the circumstances. We prefer the Jones abduction frame and have used it with much satisfaction during the acute stage (Fig. 299). It allows fixation and extension; it relieves pain and spasm, while at the same time correcting the deformity. The bed-pan may be used without moving the patient. When necessary, by grasping the bar between the legs and the head-piece, the patient and the frame may be transported without discomfort. Pressure-sores seldom develop and then only from

neglect. The body may be inspected and, if dressings are required, easy access is permitted. The length of time the patients remain on

Fig. 299.—Child on Jones abduction frame, showing extension and perineal strap.

Fig. 300.—Child sitting up first time after treatment on Jones abduction frame.

this frame is of little consequence, just so they remain long enough. It is far better to keep them there until all acute symptoms have subsided, the general condition has improved, the deformity has been corrected,

and roentgenographic examination shows redeposit of salts. Many of our patients remain on this frame a year or more when the severity of the disease, sinus or abscess-formation make it necessary (Fig. 300).

In adults the acute stage may be treated by Buck's extension in bed, the limb being supported by sandbags.

Fig. 301.—Lorenz cast which is used after Jones' frame. The sound leg is given an extension boot and crutches are used.

Fig. 302.—Modified Thomas splint used with crutches after acute stage.

During the subacute stage, if no drainage exists, a cast of the Lorenz type may be used, together with crutches and the elevation of the sound limb by means of a patten (Fig. 301).

The length of time required during this stage of treatment must be determined in each individual case. When weight-bearing is attempted under supervision and no pain ensues, the patient is warned as to the

danger of trauma, provided with a Thomas hip splint, and advised to continue crutches, for a period of three or four months, gradually applying more weight to the afflicted limb. Any remission of symptoms should be treated by recumbency and extension (Fig. 302).

At the time of examination 90 per cent of the patients in our series showed deformity, the flexion adduction type being practically always present. Nineteen per cent were ankylosed, and the average shortening was 2¼ inches. In 60 per cent the deformity was in the right hip. Ten per cent required aspiration, and 14 per cent curettage or sequestrotomy. The patients with deformities, and those in the subacute stages, were treated by brisement forcé with ether anesthesia and plaster casts, followed by crutches, etc. Osteotomy of Gant's type was performed in cases in which the deformity had become ankylosed.

REFERENCES

1. Whitman, R.: A treatise on orthopedic surgery, Phila., Lea, 1901, 650 pp.
2. Rollier: The practice of sun-cure for surgical cases of tuberculosis and its clinical results. Tr. Internat. Cong. Med., 1913, Lond., 1914, Sub.-sect. vii (a), Orthoped., pt. 2, 251–269.

WHAT ARE THE REAL RESULTS OF ARTHRO-PLASTY?*

M. S. HENDERSON

Arthroplasty is an operation designed to restore, as far as possible, the integrity and function of a joint which has been partly or totally destroyed. This report deals only in a general way with the end results of such operations in 43 cases in the Mayo Clinic and in 395 cases collected from other clinics. In some of the cases incorporated in the report the patients have been operated on for relief of bony ankylosis; others for so-called fibrous ankylosis or mechanical impediment to motion. In the collected group of cases no mention is made as to the type of ankylosis demanding the arthroplasty, but in our own cases this is stated.

Believing that a definite expression from orthopedic surgeons and their confrères concerning the end results of arthroplasties would be interesting, 180 letters of inquiry were sent out. While these opinions would be more or less general, yet being backed by a definite statement of the number of cases, they would convey a correct impression, at least, of the favor in which the operation of arthroplasty stands among the group of men on the firing-line of joint deformities.

Fifty-one answers to these letters were definite enough, so that data could be tabulated on 395 arthroplasties. The results in these cases were classified as good, fair, and poor. One hundred and twenty-six (30 per cent) of the total number of the arthroplasties were on the elbow; 117 (29 per cent) were on the knee; 98 (24 per cent) were on the hip; 30 (7 per cent) were on the jaw; and 22 (5 per cent) were on the ankle, thus showing the relative order of the frequency of operation. It seemed somewhat surprising that the number of operations on the knee closely approximated the operations on the elbow. This does not necessarily signify that operations on the knee give as good results as

those on the elbow, but because ankylosis of the knee is a more common condition, it has been very prominent in recent years as a surgical problem.

Of the 126 operations on the elbow, 97 (76 per cent) were recorded as having given good results; 21 (18 per cent) were recorded fair, and 8 (6 per cent) were recorded poor. In the 117 operations on the knee 18 (15 per cent) gave good results; 30 (25 per cent) were fair, and 69 (59 per cent) were poor. In the 98 operations on the hip-joint 56 (57 per cent) gave good results; 18 (18 per cent) were fair; and 24 (24 per cent) were poor. In the 32 operations on the jaw the highest percentage of good results was obtained; that is, 30 (93 per cent). One was reported fair, and 1 poor. In the 22 operations on the ankle the results were classified as 3 (13 per cent) good; 13 (59 per cent) fair; and 6 (27 per cent) poor.

In the total number, 395 arthroplasties, there were 204 (51 per cent) good results; 83 (21 per cent) fair; and 108 (27 per cent) poor.

Confining our attention only to those cases which were reported good, we find that the jaw ranks first, the elbow second, the hip third, the knee fourth, and the ankle fifth. Eliminating the knee-joints entirely from the compilation, there are 266 arthroplasties, in which 68 per cent gave good results; 16 per cent gave fair results, and 13 per cent gave poor results. It is plainly unfair to group arthroplasties as an entity, and each joint under discussion must stand on its own merits as to its fitness or unfitness for arthroplastic work.

The writer realizes that this collection of statistics is open to criticism, but they are offered merely to show in a general way the end-results of arthroplasties. While one surgeon may be too optimistic concerning his results, another may be too pessimistic, so that the two viewpoints tend to strike a fair average for the whole.

Our attitude in the Mayo Clinic toward the operation of arthroplasty has been frankly conservative and, considering the amount of clinical material seen in the orthopedic division, the number of arthroplasties recorded is quite small. That an excellent functionating joint can be made under certain conditions has been shown by the operation for bunions described by Dr. C. H. Mayo* years ago. In ankylosed joints the same ideal conditions do not exist, and this is particularly true if the joint in question must bear weight, for example, the knee. The question of function is primarily the most important. Many patients, not appreciating the difficulties of the operation, have requested an arthro-

*Mayo, C. H.: The surgical treatment of bunion. Ann. Surg., 1908, xlviii, 300–302.

plasty, but on having definitely placed before them the facts that the results of such operations are not certain to be good and that their ankylosed joint is both useful and painless, have gone home reconciled to their condition.

In performing an arthroplasty the basic principles and good technic must be observed to offer even a reasonable chance of success. I shall not here enter into the question of technic except to state that some of our failures may be definitely attributed to the removal of too little bone.

In our 43 cases sufficient time has elapsed since the operation to permit of a definite opinion as to the end results.

The operations on the elbow form the largest group, there being 21 cases with 12 (55 per cent) good results; 3 (13 per cent) fair; and 6 (27 per cent) poor.

The operations on the jaw form the next largest group, there being 12, with 8 (67 per cent) good results, 2 (16 per cent) fair, and 2 (16 per cent) poor.

There were 4 operations on the hip, 1 (25 per cent) with good results, 2 (50 per cent) fair, and 1 (25 per cent) poor.

Arthroplasty was done on the knee 4 times, with no good result. In 1 (25 per cent) it was fair and in 3 (75 per cent) it was poor.

The ankle was operated on twice with 1 (50 per cent) good result and 1 (50 per cent) fair result.

Of the 43 arthroplasties, we can report good results in 22 (51 per cent), in 9 (20 per cent) fair results, and in 12 (28 per cent) poor results. These results coincide in the main with the group of cases collected.

Nine of the patients having operations on the elbow had bony ankylosis and 5 gave good results. Twelve had partial though nearly complete ankylosis, 2 being subacute tuberculous cases. Good functional results were attained. One of the tuberculous patients is known to have later developed, at intervals, trivial tuberculous abscesses, but now for seven years has had a good functional joint without pain. After a fracture dislocation of the elbow a condition may ensue which is practically an ankylosis. In this particular type of case a good result is not apt to follow arthroplasty unless a great deal of bone is removed, for there is a persistent tendency to form callus after operation. In all the jaw cases there was an absolute bony ankylosis. The type of operation was merely to remove the ankylosed condyle, not placing any flap or membrane in the cavity. In all the knee-joint cases there was complete ankylosis. A good result was not obtained. In one the result was fair.

This was the case of a young woman with double bony ankylosis of the knees, and while the result has not been particularly gratifying from a surgical point of view, the patient is more than pleased with it.   There is flexion to nearly 45 degrees, and full extension, with quite a firm, steady joint.   The four arthroplasties on the hip were all done for bony ankylosis.   In one the result was good.

Conclusions

1. Statistics, taking arthroplasties on all joints as a whole, and stating percentages, are unreliable.   Each joint must stand on its own merits for arthroplastic procedures.

2. The jaw-, elbow-, and hip-joints, in the order named, give the highest percentage of good results.

3. The knee and ankle give the poorest results, and should be subjected to the operation only after very careful consideration.

43 ARTHROPLASTIES (MAYO CLINIC)

	ELBOW	KNEE	HIP	JAW	ANKLE	
Good..........	12 (55 per cent)	0	1 (25 per cent)	8 (67 per cent)	1 (50 per cent)	22 (51 per cent)
Fair..........	3 (13 per cent)	1 (25 per cent)	2 (50 per cent)	2 (16 per cent)	1 (50 per cent)	9 (20 per cent)
Poor..........	6 (27 per cent)	3 (75 per cent)	1 (25 per cent)	2 (16 per cent)	0	12 (28 per cent)
Total........	21	4	4	12	2	43

395 ARTHROPLASTIES REPORTED BY 51 SURGEONS, CLASSIFIED GOOD, FAIR, AND POOR:

ELBOW 126 (30 per cent)
KNEE 117 (29 per cent)
HIP   98 (24 per cent)
JAW   32 (7 per cent)
ANKLE 22 (5 per cent)

	ELBOW	KNEE	HIP	JAW	ANKLE	
Good..........	97 (76 per cent)	18 (15 per cent)	56 (57 per cent)	30 (93 per cent)	3 (13 per cent)	204 (51 per cent)
Fair..........	21 (16 per cent)	30 (25 per cent)	18 (18 per cent)	1 (3 per cent)	13 (59 per cent)	83 (21 per cent)
Poor..........	8 (6 per cent)	69 (59 per cent)	24 (24 per cent)	1 (3 per cent)	6 (27 per cent)	108 (27 per cent)
Total........	126	117	98	32	22	395

OSTEOCHONDROMATOSIS OF THE KNEE-JOINT*

M. S. HENDERSON

It is generally recognized that loose bodies in the knee-joint may be produced by direct trauma to the articular surfaces of the joint. It is also recognized that in a certain group of persons suffering from osteochondritis dissecans there is a tendency to the formation of these loose bodies on the infliction of a comparatively slight trauma. In such instances the bodies rarely exceed two or three in number. Occasionally, however, a history is obtained of a locking of the joint (usually following trauma), and on physical examination the knee-joint gives the sensation of feeling a sack of marbles, so numerous are the loose bodies. The skiagraph shows perhaps 25 or more bodies in a distended synovial sac, but the joint surfaces themselves are clear cut and show no scarring to give us a clue to the origin of the bodies. It appears that the joint has a pathologic habit of producing loose bodies in such numbers that "osteochondromatosis" best describes the condition. The term is more restricted than "loose bodies," and is distinct also from that of osteochondritis dissecans.

The following case is an example of osteochondromatosis of the knee-joint.

CASE 157963.—A male, aged twenty-six years, single, oil-well driller, presented himself for examination at the Mayo Clinic April 21, 1916. The complaint was locking of the left knee, followed by disability, pain, and swelling. His family history and personal history were negative. Past illnesses were pneumonia ten years before, and gonorrhea thirteen years before. He denied syphilis, and the Wassermann test was negative. Ten years before his leg was violently twisted outward and "dislocated." A companion pulled on the leg and it "went back into place" with a loud snap. He was incapacitated for a few days; marked swelling followed and persisted to an appreciable degree for six months. During this time the knee could be completely flexed, but not completely extended. Soon after he noticed that something jammed in the

posterior part of the joint, locking it in a slightly flexed position.   By
flexing still farther and
manipulating the leg a
little, the joint would be-
come released.   Gradually
during these years the at-
tacks became more painful
and more frequent, each
one disabling him for about
a week.   He developed a
feeling of insecurity of the
knee, and was always fear-
ful of an attack.   His work-
ing efficiency was reduced,
and, finding it difficult to
hold a position, he came to
the Clinic seeking relief.

Fig. 303.—Multiple loose osteocartilaginous bodies in knee-joint.
Note distended suprapatellar pouch.

The physical examina-
tion showed a well-devel-
oped man, 5 feet, 11 inches
in height, weighing 165
pounds.   The examination was negative, with the exception of the left
knee, where multiple loose bodies
could be felt; motion of the left knee,
at the time of our examination, how-
ever, was normal.   A roentgenogram
showed shadows of multiple loose
bodies extending up the inner and an-
terior aspect of the femur, well above
the level of the patella, in the dis-
tended suprapatellar pouch; many
were present in the posterior pouch,
in the notch between the condyles
(Fig. 303).   Hypertrophic arthritis
was also present.

Fig. 304.—Loose bodies (19) removed from
anterior compartment of the joint by the median
incision.

On April 27, 1916, the patella was
split longitudinally, the joint exposed,
and 19 roughly rounded loose bodies,
varying in size from $3/8$ to $3/4$ inch,
were removed (Fig. 304).   As many
as possible were forced from the pos-
terior compartment, but the majority
in this position defied all efforts to
dislodge them.   They were rough and
mulberry-like in appearance.   A considerable degree of hypertrophic
arthritis was made out at the articular margins, and this was carefully

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examined to detect a possible origin in the lipping for the loose bodies. The arthritis was not very marked, and, in my opinion, was produced secondarily by the mechanical action, and could not have been the primary cause of the loose bodies. My reason for this opinion was the picture presented by the synovial membrane, which was loose, wrinkled, pouched, and somewhat congested. Multiple fibrous tags hung from the synovia of the capsule, the articular surfaces themselves being normal in appearance except for a low degree of hypertrophic arthritis presenting at the edges as stated. These fibrous tags varied in size, both in diameter

Fig. 305.—Loose bodies left in the posterior compartment of the joint. Apparently six in number.

and length. Some were pedunculated and the tips of the bulbous ends were covered with cartilage. It was very clear that the loose bodies were produced by the growth of the cartilaginous-tipped tags until they became too heavy for the pedicle, when they broke loose and wandered about the joint as free bodies, gradually increasing in size, being nourished by the joint fluid. One of these hanging cartilage-tipped tags was excised, and a microscopic section showed the synovial membrane congested at the base, the pedicle fibrous, and the tip cartilaginous. One of the mulberry-shaped osteocartilaginous bodies was sectioned for microscopic study. There was bone in

Fig. 306.—Loose body still remaining after removal of six bodies by posterior incision.

the interior, distributed at random in small flakes and surrounded on all sides with cartilage.

The patient's convalescence was satisfactory, except that effusion persisted. He was told that all the bodies were not removed, and that an incision into the posterior compartment would be necessary. On attempting to use the leg, recurrence of the locking was produced. A roentgenogram (Fig. 305) showed loose bodies, probably six in number, in the posterior compartment.

On June 23, 1916, the joint was explored by a posterior incision after the method described by Brackett and Osgood, and six good-sized loose bodies were removed. A diligent search was made, but others could not be located. The convalescence was satisfactory, but another roentgenogram on July 3, 1916, showed one loose body still in the posterior compartment (Fig. 306). The plate was shown to the patient and he was advised to return for the removal of the body if he had any further trouble.

The etiology is the most interesting phase of the subject under discussion. Osteochondromatosis is not limited to the knee-joint. I have seen two cases in which the elbow-joint was involved. Both were operated on. Riedel reports one case in which the wrist-joint was involved; Rehn, one of the elbow-joint; and Troell, one of the hip. Reichel recorded the removal of two handfuls of loose bits of cartilage from the knee of a man aged thirty-six years. Since the articular surfaces of the tibia, femur, and patella were normal, he considered that the capsule was the source, but that inflammatory reaction was the exciting agent. The appearance of the synovia, according to his description, was similar to that of the case herein reported. Kopp, in an excellent article, reports three such cases, with a discussion of the etiology that is both interesting and clear.

The theory of Barth, König, and Ludloff, regarding the production of loose bodies, is that trauma is the important factor, though there may be an idiosyncrasy in some persons toward the formation of loose bodies, as in osteochondritis dissecans. Reichel, as I have before mentioned, is of the opinion that the whole pathologic condition in the joint is due to some inflammatory process, but Kopp and others find no support for this theory. On embryologic grounds Lexer advances the theory that embryonic rests of cartilage remain which are responsible for the production of such bodies. Müller believes that the line of demarcation between the periosteum and capsule is the site of the origin of these bodies. Kopp and Langemak are of the opinion that they arise from the capsule itself. Kopp says he finds the proliferation "exclusively in the synovia just under the epithelial layer."

It also might be considered as not improbable that many osteal and chondromatous cells are forced into the joint fluid at the time of the original injury, such as was sustained by the patient whose history is presented in this paper. Certain of such cells might coalesce and grow, producing finally many good-sized loose bodies. However, this theory would not adequately account for the pedunculated condition of the synovia, with many of the synovial excrescences covered with cartilage.

From a clinical point of view, loose bodies may be produced in the knee-joint in any one of three ways:

1. In a normal healthy knee-joint direct trauma, such as falling on a hard, rough substance with the knee flexed, may be the cause. The object on which the person forcibly kneels may strike the internal condyle of the femur with sufficient force to chip off a piece of the cartilage, and possibly a piece of the underlying spongy bone. This may immediately desiccate or hang for a varying length of time, and later become a loose body. The roentgenogram usually shows the scarring of the condyle, and the loose body occasionally may be seen resting in this spot. There being no history in these cases of an idiosyncrasy to form loose bodies, it may be assumed that they are truly the result of trauma.

2. Another group of cases is known as osteochondritis dissecans. Trauma, not necessarily direct and often most trivial in character, is a definite factor in these cases also. For some unknown reason, a comparatively mild trauma to these joint surfaces that are unnaturally brittle will cause a certain area to desiccate and become a loose body. König had a theory that in some way the arteriole to an area on the outer side of the internal condyle at the insertion of the posterior crucial ligament becomes plugged, and this area, deprived of its nutrition, sloughs off to wander in the joint. In many ways this theory seems the most plausible. Bodies formed in this manner may be multiple; however, they do not usually exceed two or three in number. In not a few instances I have seen the condition in both knees. The roentgenogram, if taken at the right angle, here also shows the scarring of the joint surfaces. I have never seen these bodies arise except from the condyles (usually the internal) of the femur.

3. Osteochondromatosis forms a smaller group of cases in which the bodies are in greater numbers and cannot be accounted for by the conditions in either of the foregoing groups. In the case described, the findings at operation pointed to a synovial origin, as advanced by Kopp, Langemak, and Whitelocke. Kopp holds that these bodies start as os-

teomas and not osteochondromas, because in his cases no cartilage was found about the smaller bodies. He explains the cartilage on the larger bodies on the ground that they originated near the point where the synovia is reflected from the cartilage ends of the bone.

Whitelocke believes that fibrous tags hanging from the synovial membrane become cartilaginous, and that the development of fibrous tissue into cartilage is due to the fact that the early development of the synovial membrane, the articular and interarticular cartilages of the knee-joint, are all from the same primitive embryonic intermediate layer of the axial blastema.

In the case I am reporting there was a history of severe trauma at the onset. Whether this is always to be elicited in cases that may be called osteochondromatosis, I cannot say. In the cases reported by Kopp (three in number), there was a history of trauma in two—one very slight, the second more severe. In the third there was no history of trauma. It is evident that it is some condition in the synovial membrane which leads to the formation of the osteocartilaginous bodies. I have seen a like condition in the knee of a man who had a tumor of the lower end of the femur. The roentgenogram revealed also multiple loose bodies in the knee-joint. The specimen removed from the femur at operation showed the tumor to be the osteochondroma type, the cells not appearing malignant. In this instance the synovial membrane of the joint apparently was participating in the new growth. The synovia was hypertrophied and pouched. In places the pouches were pedunculated, with the tips becoming cartilaginous; some were of good size, being larger than a pea. The new-growth from the bone had already broken through into the joint by way of the internal condyle, forming an exostosis in the joint cavity itself. After operation the tumor rapidly recurred and increased in size. A second specimen showed a mix-celled sarcoma, and amputation was performed. When the patient was dismissed, the roentgenogram showed metastasis in the lungs. He was greatly emaciated and clearly had not long to live.

It may well be that osteochondromatosis is a form of new-growth which is not malignant. This theory is more tenable than that the condition is due to infection.

REFERENCES

Barth, A.: Zur pathologischen Anatomie der Gelenkmäuse, Centralb. f. Chir., 1895, xxii, 977–980.
Brackett, E. G., and Hall, C. L.: Osteochondritis dissecans, Am. Jour. Orth. Surg., 1917, xv, 79–94.

Brackett, E. G., and Osgood, R. B.: The popliteal incision for the removal of mice" in the posterior capsule of the knee-joint. A report of cases. Bosto and Surg. Jour., 1911, clxv, 975–976.

Freiberg, A. H., and Wooley, P. G.: Osteochondritis dissecans; concerning its n: relation to formation of joint mice. Am. Jour. Orth. Surg., 1910–1911, viii

König: Ueber freie Körper in den Gelenken. Deutsch. Ztschr. f. Chir., 1887 90–109.

Kopp, J. W.: [Osteochondromatosis.] Nederl. Tijdschr. v. Geneesk., 1916, ii

Langemak: Cited by Kopp, loc. cit.

Lexer, E.: Lehrbuch der allgemeinen Chirurgie, Stuttgart, Enke, 1908, i, 357

Ludloff, K.: Zur Frage der Osteochondritis dissecans am Knie. Arch. f. kli lxxxvii, 552–570.

Müller, W.: Demonstration zur Gelenkpathologie. Versamml. deutsch. zu Breslau, 1904, Sekt. f. Chir.; Zentralbl. f. Chir., 1904, ii, 1398

Rehn, E.: Gelenkchondrome, Beitr. z. klin. Chir., 1911, lxxi, 817–831.

Reichel, P.: Chondromatose der Kniegelenkkapsel, Arch. f. klin. Chir..

Riedel: Cited by Kopp, loc. cit.

Ridlon, J.: Osteochondritis dissecans. Jour. Am. Med. Assn., 1913.

Troell, A.: Zur Kenntnis der Entstehung von freien Körpern im K: derer Rücksicht auf die sogen. Osteochondritis dissecans. Arc cv, 399–417.

Whitelocke, R. H. A.: Loose bodies in the knee, with special ref and growth. Brit. Jour. Surg., 1914, i, 650–664.

TRENCH FOOT*

(A Review of the Literature of the Etiology and Pathology)

L. B. WILSON

Definition.—Trench foot is the new name of the well-known condition of chilblains and frozen feet. Essentially it consists of various degrees of stasis of blood in the feet, due to several causes, of which cold is the predominating factor.

History.—In civil life, chilblains and frost-bite are common in all cold countries, particularly among new arrivals who are not acclimated and who have not yet learned how to take care of themselves. In military service every army fighting in unfamiliar cold and wet climates since war began has suffered from the condition. In modern times the first good general description of frosted feet is that by Baron Larrey, Napoleon's chief surgeon, in 1812. His observations were extensive and his deductions as to the cause, the essential pathology, and the principles of treatment have been but little improved on in a hundred years. In the Crimean war frost-bite was very prevalent among the English troops,—more than 2000 men being invalided therefor,—while the French suffered in still larger numbers as well as more severely. Though our Civil War was fought in a relatively warm climate by soldiers who wore loose trousers without leggings and many of whom, as civilians, had been accustomed to take proper care of themselves in severe outdoor conditions, yet the *Medical and Surgical History of the War of the Rebellion* contains records of many amputations of the toes and feet for gangrene following frost-bite. The Balkan wars were largely wars of movement rather than position, yet hundreds of cases of frost-bite were reported in the Turkish, Bulgarian, Greek, and Servian armies. The present war, except for the first few months, and especially on the French and Belgian fronts, has been a war of position to a greater extent than any previous conflict. It has been fought largely in water-soaked

trenches, almost or quite freezing cold in winter, by men with bandaged legs and with little freedom of movement. As a result, it has yielded a perfectly appalling number of temporary and permanent disabilities from trench foot. During the winter of 1914–1915 a number of British observers each reported from 100 to nearly 5000 different cases. Out of 160 patients admitted to the British Red Cross Hospital at Boulogne, France, in one evening, 120 cases were of frost-bite alone, and many of them were stretcher cases. Preventive measures during the last two winters have reduced the number considerably, and yet hundreds of cases probably will be reported in 1918. The prospects are that the highest percentage will be among our own men—the newest comers in France—unless vigorous preventive measures are taken at once.

Predisposing factors.—The predisposing factors of long standing are conditions of enfeebled circulation and lack of acclimatization to cold. Underfeeding, especially a lack of hydrocarbons and carbohydrates, diarrheas, loss of sleep, and the excessive use of tobacco, as noted by Fearnsides, are all important predisposing factors in so far as they affect the amount or quality of the circulating blood. Lack of acclimatization to cold has been noted as an important predisposing factor by a number of observers. One medical officer with a large experience reports that approximately half his cases came from five regiments recently returned from India, Egypt, and Malta, a percentage more than five times that from other regiments under similar conditions. The possibility of inuring the surface of the body to cold was well illustrated among the North American Indians prior to civilization. Many Chippewa children played naked in the snow, and their elders hunted in winter with little or no clothing, in northern Minnesota, within the memory of men still living. The bare legs of Highlanders and the exposed throats and chests of women are similar illustrations. Any portion of the skin of the body may be gradually made as resistant to cold as is the face, the only conditions being that too large a surface shall not be exposed for too long a time, that the supply of heat-producing food shall be large, and that vigorous muscular activity shall be maintained.

Immediate causes.—The immediate causes of trench foot are all those factors which tend directly to produce blood-stasis in the feet. The chief of these is cold. Lake has shown that the reduction of the soft tissues of the human body to a temperature of -6 C. (equals $+21$ F.) or lower produces true freezing and direct damage to the tissues by cell destruction. Degrees of cold above this critical temperature only pro-

duce their ill effects by vasomotor paralysis. Most of the cases of trench foot in the present war have occurred at temperatures above freezing, and this has accounted in a large measure for the early confusion in identifying the condition as parallel in all its pathology with true frost-bite. Wet clothes rapidly extract heat from the body. During the first winter of the war many soldiers stood for hours or even for several days in cold mud and water, commonly up to their ankles, and not in-frequently up to their knees and hips, with no protection other than that of their ordinary uniforms. Under such circumstances the abstraction of heat from the extremities is extremely rapid and the consequent vaso-motor disturbances very great.

Waller and Rideal lay emphasis on the prolonged action of water on the skin. They state that "workers in paper manufactories who stand in several inches of warm water and paper pulp for a day at a time have symptoms similar to those of fishermen and otter hunters who stand for several hours in cold water." Since they found experimentally that salt water has less effect on the skin than fresh water, and that recovery is more rapid, they recommend the prophylactic use of an ointment of lard or tallow with 4 to 10 per cent of sea-salt.

Besides cold and wet, probably the most important immediate factor in the causation of trench foot is the absence of muscular contractions. Osler has written a brief article entitled "Cold-bite+Muscle-inertia= Trench Foot," in which he notes that "the disabling effects of cold bite are inevitable in feet attached to legs whose muscles have not play enough to maintain circulation hampered by cold and wet."

The mechanical pressure due to tight puttees, leggings, and shoes is a large causative factor. That crime against common sense, the spiral puttee, shrinking as it does as much as one-sixth its length when wet, especially has had many victims. The effect of tight shoes is shown by necroses and gangrene over areas where they have brought pressure, though it must be noted that the same areas are apt to be most affected even when not subjected to external pressure.

Hughes says that the usual position the men assume in the trenches while sitting on the firestep with their legs hanging over and feet un-supported, thus bringing considerable pressure over the popliteal space and impeding the return of blood along the popliteal vein, may be an important immediate causative factor.

Finally, however, it is of utmost importance to recognize that the chief demonstrable lesions in the affected tissues and those which are

responsible for the pain, swelling, discoloration, ulceration, and gangrene of the feet are not due to primary injury from the cold, but to the too sudden reëstablishment of the circulation, with its resultant paralytie dilatation of the vessels, intense exudation, and circulatory stasis leading to malnutrition.

Symptoms.—Lawson says the cases may be divided clinically into those in which there is something to see with little or nothing complained of, and those in which there is nothing to see but a varying amount complained of. In the first group are conditions varying from mere hyperemia of the skin to actual sloughing of the subcutaneous tissue. In the second group there are sensory phenomena—paresthesia, hyperesthesia, hyperalgesia, analgesia, and anesthesia. Externally, three degrees of severity may be recognized: first, a transitory erythema, usually disappearing rapidly; second, the formation of blisters beneath which necrotic areas of skin often exist, and in which ulcers sometimes develop; and third, gangrene.

The chief complications are those due to infection with pyogenic cocci, gas or tetanus bacilli. Raymond and Parisot believe that a large share of the more complicated symptoms are of microbic origin. They have isolated an organism, which they find chiefly in the purulent layer of the vesicles, which injected into the skin of the rabbit and guinea-pig gives rise to lesions similar to those exhibited in man.

Diagnosis.—Ordinarily the condition is readily diagnosed from the appearance of the affected limb, though, as has been noted above, there are cases in which little is to be seen. Soldiers so affected must be distinguished from malingerers whose "cold feet" are merely a mental state.

Pathologic anatomy.—The blood stasis due to cold begins as an anêmia, followed by hyperemia, exudation, capillary hemorrhages, vesication, malnutrition, and gangrene. Though the general pathology of frost-bite has been clear for many years, the investigations of Smith, Ritchie, and Dawson, Lake, and others have materially increased our knowledge of the histologic conditions present. The first-named observers conducted a series of experiments on rabbits in which they showed that the exposure of the rabbit's feet to cold mud sets up conditions parallel to those in trench foot. They found further that:

"Two turns of adhesive plaster around the limb greatly increases the amount of edema, and that when the tissues had been damaged by exposure to cold, edema was rapidly set up, or, if already present, was

greatly increased by placing the animal's feet in water at a temperature of 37 C. (98.6 F.). The histologic examination of the tissues of the feet showed that the chief effect was on the blood-vessels. In these there were dilatation of the lumen, swelling of the endothelium of the intima, and vacuolation in the muscle-fibers of the media. There was also increase in the number of cells of the perivascular tissue. There was no evidence of thrombosis in the vessels. The lymphatic vessels in some cases were unaltered; in others, they were·dilated; and in others they were filled with masses of cells and fibrin. In the tissue spaces the chief changes noted were: (a) Swelling and separation of the fibrils of the collagen bundles; in some areas where the fibers were widely dissociated they were undergoing solution in the exudate; (b) among the bundles there was a copious deposit of fibrin in the form of granules or of a network of beaded filaments. Fibrin granules and threads were also seen inside some of the blood-vessels and lymphatics; (c) in cases, especially where edema had been present for some time, there was an abundant diffuse infiltration of the tissue with leukocytes; (d) in cases where the foot was subjected to warm water, the congestion was followed by a diffuse infiltration with red corpuscles; in some cases this passed into actual hemorrhage—the damaged blood-vessels giving way under the strain of the congestion caused by the warmth.

"Generally a few staphylococci were found in the tissues of the feet. These were probably derived from the skin. While they increased in number, they had not acted in any way as foci of inflammation. Their presence in the tissue was probably a sign of the devitalizing effect of the cold.

"The changes in the nerves consisted in the edematous swelling of the axis-cylinders, and this seemed to be merely a part of the general edema of the foot or ankle.

"The changes noted in the voluntary muscles consisted of a modification in their staining reaction, loss of striation, and in cases of longer duration, infiltration with leukocytes, and a slight deposit of fibrin between the fibers. In muscles which had been actually frozen, these changes were more advanced.

"The regional lymph-glands were enlarged from dilatation of the sinuses and hypertrophy of the follicles. The sinuses contained fibrin deposited in the form of granules and threads, and in the network formed by these were lying red corpuscles, polymorphs, and proliferated endothelial cells. There was no evidence of the presence of micrococci."

Their general conclusions are:

"It is clear from experimental investigations that the essential change consists in the damage to the blood-vessels. There is probably an initial constriction of the vessels, but when this passes off it is because of their damaged condition that the swelling of the feet occurs while the circulation is being restored to normal. The damage is evidenced by the swelling of the endothelial cells in vessels of all kinds and by the vacuolation of the muscle-fibers in the arterial walls. An excessive amount of fluid is consequently poured out into the tissues, and in some cases the vessels rupture and hemorrhage follows. Along with the injury to vessels there is also an interference with the vitality of the cells of the surrounding connective tissues. Evidence of this is found in the readiness with which the fibrin formation occurs in the exuded fluid as contrasted with its absence in the form of thrombi in the blood-vessels. Further evidence of injury is the infiltration of the parts with leukocytes and other phagocytic cells whose function is the removal of the products of tissue destruction.

"If the results of our experiments on the application of moderate wet cold for long periods be compared with what we observed as the result of very low temperatures acting for a short time, it will be found that no difference except in degree exists between the effects produced in the two cases. When extreme cold does not immediately kill the tissues, the resultant changes are practically identical with those of the longer application of the milder irritant.

"The relatively greater effect of wet cold as compared with that of dry is no doubt due to the fact that water is a much better conductor of heat than air.

"All our clinical observations can, we think, be rationally interpreted in the light of our experimental results. The swelling and redness are essentially the effects of an injury to the vessel-walls, which, when the circulation is restored, originates what is in essence an inflammatory reaction; the unusual resistance of the edema to pressure is evidence of the presence of a semisolid fibrinous deposit; the slighter degrees of blackening of the skin arise from diffuse interstitial hemorrhage from the injured vessels, such as we have experimentally produced—its evanescence is corroborative of its not being an evidence of true gangrene; the supervention of superficial or deep ulceration is an indication of the presence of a cellular necrobiosis which, if severe in degree, may go on to cellular or even gross necrosis; the slowness of the recovery, even when

actual necrosis is not present, points to the occurrence of a regeneration, such as our observation of experimental lesions would lead us to anticipate; the limitation of the nervous symptoms to the region of actual inflammation has its explanation in the absence of definite nerve changes in the artificial lesions, and leads us to attribute these symptoms chiefly to the external and secondary effects of the exudation.

"The nature of the changes produced sufficiently explains the slowness of the recovery in man. For this to be complete, not only must there be subsidence of the swelling, but there must be a restoration of the vessel-walls so that they can bear the strain of the changes in the circulation which take place in ordinary forms of activity, e. g., walking. There must be also a clearing of exudates from the lymphatic paths, and both processes require time. Hence it is only found that, even when the swelling has disappeared, pain, tenderness, and disturbance of feeling still persist; the patient is unable to walk about freely, and any application of warmth to the feet tends to bring back the symptoms."

Lake, from a recent series of experiments on the effect of cold upon tissues under various conditions, concludes that:

"In the production of trench foot cold must be considered the essential factor, other factors being either secondary or subsidiary."

"The use of vasoconstrictors delays the swelling in cases of true frostbite, while in cases of chilling the exhaustion may be entirely prevented."

Treatment.—The first treatment applied to trench foot, if improper, may cause so much tissue damage and so much suffering that its consideration is extremely important. The main principle of treatment has been for years a matter of common knowledge. Our only wonder is at the fact that some army medical officers have disregarded the principle. It was happily stated by Gross as long ago as 1859. He says: "The great indication is to recall the affected parts gradually to their natural condition by restoring circulation and sensibility in the most gentle and cautious manner, not suddenly or by severe measures. All warm applications, whether dry or moist, are scrupulously refrained from; the patient must not approach the fire, immerse his limbs in warm water, or even be in a warm room."

Though every school-child in the cold Northwest knows that he should rub his frosted ears with snow rather than hold them to the fire, hundreds of men with trench foot were told by their medical officers, as well as their line officers, to warm their numbed feet at the fire or to wash them with warm water. In an article published as late as June, 1915, in the London *Lancet*, a surgeon writes:

"The feet should be well covered with voluminous dressings of cotton-wool. The wool should be four or five layers deep, loosely and thoroughly envelop the whole of the foot, and extend up the leg beyond the area of pain and tenderness." Numerous other authors advocated the use of various forms of hot baths, stimulating local applications, and manipulations and general medication (including the administration of thyroid extract!), all having for their object the rapid restoration of circulation in the affected limbs. In May, 1915, Sir Berkeley Moynihan in a brief note vigorously called attention to the importance of leaving off dressings. He said: "Parts affected should be smeared with some ointment, covered with a thin layer of gauze, the feet raised a few inches from the bed upon a hard pillow, and the lower part of the legs and feet covered in bed only by a sheet. Pain is almost exactly proportionate to the degree of warmth of the foot. The relief of pain should be our chief consideration."

The treatment of complications, infections, gangrene, etc., should be along ordinary lines and needs no comment here except a warning to surgeons not to be too hasty in advising amputations. It is a common experience that many frozen feet in which gangrene has developed to an apparently hopeless degree may be saved by giving nature a chance. The skin and subcutaneous tissues may slough off slowly and leave very good feet, with or without subsequent skin-grafting.

Prognosis.—In cases of mild and moderate severity patients, if properly treated initially, get completely well of themselves, but, even in mild cases with bad primary treatment, they are left with permanent hypersensitiveness (chilblains) and a tendency to recur with subsequent slight chilling. The changes in the vessels of the legs may be so great that chronic ulcers persist for years following amputations of the feet for gangrene.

Prevention.—Preventive measures obviously are to be directed to keeping the extremities warm and the blood circulating in them. The British Army Routine Order No. 353, of November 23, 1914, gives the following precautions:

"1. Boots should not fit tightly; should at least be a size too large. When large boots are worn, it is well to wear two pairs of socks, but this is dangerous if the boots are small, as it leads to further pressure on the foot. Puttees should never be applied tightly.

"2. The general circulation can be kept up by keeping the body warm and dry. A mackintosh sheet worn over the great-coat is of assistance when no water-proof is available.

"3. A dry pair of socks should be carried in the pocket when available.

"4. The officer should see that dry standing is provided in the trenches whenever possible by means of drainage, raising of the foot level by facines of brush, wood, or straw, with boards on top, or by the use of pumps, when these are available."

Recently the more permanent trenches in many cases have been floored with latticed foot-walks—so-called duck-boards.

Leggings and puttees under conditions of cold and wet should be abandoned. There is no doubt that the soldiers in our Civil War escaped frosted feet to a very great degree because they wore loose fitting trousers and the circulation was unimpeded by tight clothing around their ankles. The Swiss soldiers, trained in a country with much snow and ice, wear no leggings or puttees, but loosely overlap and button the cuffs of their trouser legs near the ankle. The northern lumberjack, working throughout the winter in deep snow in extremely cold weather, wears two or three pairs of woolen socks in loosely laced shoes, but rolls up or cuts off the legs of his trousers well above the shoe-tops. Tradition in lumber camps has developed a system of foot protection marvelously efficient. The lumberjack takes more time to dress his feet in the morning than he does to dress the rest of his body. His shoes and socks are carefully dried every night. His boots, with heavy rubber bottoms and well-oiled eight-inch leather tops, are excessively oversize. When his feet are numb, he kicks and dances. If they are frosted, he takes off his shoes and socks and walks in the snow. As a result of these precautions frosted feet are almost unknown in the northern lumber camps.

Delepine, as the result of extensive experiments, recommended in 1915 the use of leg-bags of silk, waterproofed with oxidized linseed oil, for protection. These are worn over the socks inside the boot and inside the trousers. Many thousands of these have been issued to the British troops. In Germany the Special Military Committee for Warm Underclothing, formed at the suggestion of the Empress, has sent to the soldiers thousands of yellow, oiled, and waxed paper covers to go on the foot inside the boot. While I have seen no detailed report on the use of either the English oiled-silk bags or the German waxed paper leg-bags, it is probable that they have proved only temporarily impervious to the water, and that when once water does get into them and soaks the contained socks and underclothing, they give practically no protection from the cold, being themselves fairly good conductors of heat.

Covering the feet and the legs with grease, such as tallow, linseed oil, vaselin, etc., is a common preventive measure against wet and cold. Lumberjacks, when long exposed to ice-cold water while river-driving logs, not infrequently paint their feet and legs with zinc oxid paint. Such preparations serve to a very limited extent only as non-conductors, and act chiefly in preventing maceration of the skin, with consequent constriction of the surface capillaries.

Both clinical experience and animal experiments have shown that prolonged exposure to moderate degrees of cold and wet is quite as bad as short exposure to extreme degrees. Therefore, the length of service of soldiers in the trenches, if possible, should be shortened when their feet are wet and cold. Soldiers in trenches must be encouraged to keep the muscles of their limbs moving as much as possible when their feet are cold and wet, thus greatly aiding circulation. Hughes, by insisting that the men of his regiment should, when resting at night, lie with their feet on the firestep, cut down his cases of trench foot to a negligible quantity.

Heat-producing food must be provided in as large quantities and in as appetizing and digestible condition as possible.

Men should be warned of the danger of the overindulgence in tobacco, since it paralyzes the nerve-ends of the vasomotor nerves.

The whole matter may be summed up in the three directions: Keep the feet as warm and dry as possible and keep good blood circulating in them. If overchilling does occur, reëstablish circulation slowly and not by warm applications.

An excellent article just published by "A Military Observer" reprints the leaflet issued by the British army on "Chilled Feet and Frostbite," as follows:

"Experience in the worst part of the line shows that where effective preventive measures are taken, the so-called trench foot does not occur. The occurrence of even a single case in a battalion is therefore a reproach to the unit concerned. The following preventive measures will be adopted forthwith:

"1. *Foot Preparation Rooms.*—Each brigade will provide rooms in which the feet of men will be washed in tepid water and rubbed before proceeding for a tour of duty in the trenches. The A. D. M. S. will provide personnel for supervision of these rooms.

"2. *Drying Rooms.*—Each brigade will arrange for rooms in which clothing, socks, and puttees can be thoroughly dried and dry socks provided on the return from trenches.

"3. *Provision of Dry Socks.*—A pair of dry socks for each man will be sent to the trenches with the rations daily. Wet socks will be sent back to transport lines by ration-carrying parties. Socks will be sent up in waterproof boxes or bags.

"4. *Fitting of Socks.*—Socks must not fit tightly and should be inspected as carefully as boots.

"5. *Care of Ankle Boots.*—Company officers will see that the following precautions are taken regarding boots: (*a*) Sound laces will be provided to facilitate taking off of boots, as knotted laces delay or prevent removal. (*b*) Boots will be dubbened outside to keep out wet. (*c*) Boots will be fitted loosely. (*d*) Boots will be laced loosely. (*e*) Boots will be kept in good repair.

"6. *Care of Gum Boots.*—Brigades will make arrangements for the drying of gum boots. Officers commanding will be responsible that gum boots are properly stored when not in use. They must not on any account be left on the ground outside dugouts.

"7. *Care of Puttees.*—Puttees must always be applied loosely, and when they become wet, must be taken off and reapplied, as they shrink on becoming soaked with water.

"8. *Removal of Boots in the Front Line Trenches.*—Platoon commanders must arrange for each man to take off his boots at least once in twenty-four hours. A scheme will be worked out for men to do so in rotation, even if it is necessary to sit on the parados at night.

"9. *Stamping Exercises.*—Circulation will be kept up by stamping when possible and keeping the men employed in various ways. Nothing is more conducive to trench foot than standing about.

"10. *Personnel for Supervision of Preventive Measures.*—Regimental stretcher-bearers will assist company commanders in the supervision of preventive measures, and two men per platoon will be trained by regimental medical officers in foot massage. On relief after a spell in the trenches these men will be sent ahead to rest and be prepared to start operations as their platoon arrives.

"A trained masseur of the R. A. M. C. will start a course of instruction of foot massage for regimental stretcher-bearers forthwith.

"11. *Hot Food and Drinks.*—The provision of hot food and drink is of first importance in the prevention of the conditions which predispose to trench foot.

"Officers commanding will arrange for their men to have at least two hot meals a day; for preference, one in the middle of the day and one between midnight and 5 o'clock A. M. Food containers of the Thermos variety are available, and should be used to the fullest extent. They can be readily supplemented by petrol tins placed inside a double-chambered wooden box with a layer of sawdust between the two boxes. Two two-gallon petrol tins used in this way will give 64 men half a pint of hot soup or cocoa each.

"12. *Transport Lines.*—Men working in the wet transport lines of

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the Ypres salient require consideration only next to that of men in the trenches.

"Transport officers will see that the precautions outlined above are carefully observed.

"13. *Anti-frost-bite Grease and Whale Oil.*—All ranks must clearly understand that the grease or oil supplied is merely a lubricant to facilitate rubbing of the feet. The grease has no inherent quality, and merely smearing the feet is worse than useless. The feet must be rubbed until all grease or oil has disappeared and they are quite dry.

"14. *Feet Inspection.*—Platoon commanders must be made to realize that the condition of their men's feet is as important as the condition of their rifles, and that feet inspections are just as essential in trench warfare as in marching tests. A good platoon commander should be as familiar with the condition of his men's feet as he is with the cleanliness of their rifles."

TRENCH SHIN

Though most observers describe the condition commonly known as "trench shin" as part of the syndrome of "trench fever," Chambers has attempted to differentiate it therefrom. For the present, however, the discussion must be left to those personally familiar with the condition.

REFERENCES

Chambers, G.: Trench Shin an Infectious Fibrositis. Lancet, 1917, i, 752–755.
Delepine, S.: Prevention of frost bites. Lancet, 1915, i, 271.
Delepine, S.: Some of the effects of exposure to wet cold and their prevention. Brit. Med. Jour., 1915, ii, 788–892.
Delepine, S.: Contributions to the study of the cause and prevention of trench foot so-called. Internat. Jour. Surg., 1916, xxix, 173; 217.
Fearnsides, E. G.: Frost bite. Brit. Jour. Dermat., 1915, xxvii, 33–51.
Gross, S. D.: A system of surgery. Phil., Blanchard, 1859.
Hughes, B.: The causes and prevention of trench-foot. Brit. Med. Jour., 1916, i, 712–714.
Lake, N. C.: An investigation into the effects of cold upon the body. Lancet, 1917, ii, 557–562.
Larrey: Mémoire sur la gangrène seche causée par le froid ou gangrène de congélation. Campagne de Pologne. In his: Mémoires de chirurgie militaire et campagnes. Edition Smith and Buisson, 1812.
Lawson, C. B.: Frost bite. Brit. Jour. Surg., 1914–15, ii, 703–705.
Medical and surgical history of the War of the Rebellion. 1870–88. Vol. 3, Pt. 2, Surg., pp. 671–678.
Moynihan, B.: Frost bite. Lancet, 1915, i, 401.
Osler, W.: Cold-bite+muscle-inertia=trench-foot. Lancet, 1915, ii, 1368.
Raymond, V., and Parisot, J.: Etiologie, prophylaxie et thérapeutique de l'affection dite gelure des pieds. Compt. rend. Acad. d. sc., Par., 1916, clxii, 694–698.
Raymond, V., and Parisot, J.: Étude sur le pied de tranchée (gelure des pieds). Bull. et mém. Soc. méd. d. hôp. de Par., 1917, 3 s., xli, 327–361.
Smith, J. L., Ritchie, J., and Dawson, J.: On the pathology of trench frost-bite. Lancet, 1915, ii, 595–598.
Smith, J. L., Ritchie, J., and Dawson, J.: Clinical and experimental observations on the pathology of trench frost-bite. Jour. Path. and Bact., 1915–16, xx, 159–190.
Waller, W., and Rideal, E. K.: Report on "trench foot." Jour. Roy. Army Med. Corps, 1916, xxvi, 635–641.

TECHNIC

THE TREATMENT OF ELEPHANTIASIS BY THE KONDOLEON OPERATION*

W. E. SISTRUNK

Several years ago Kondoleon, of Greece, described an operation which will probably occupy an important position in the future surgical treatment of lymphatic obstruction. His report of the results obtained by the method, and the case reports which have been published by several surgeons in this country who have used it (Matas, Royster, Hill, and others), have been sufficiently encouraging to make it appear that relief may now be offered to many patients of a class which formerly has failed to respond to the other methods of treatment.

Until this method was suggested we did not possess any means of satisfactorily dealing with many patients suffering with elephantiasis and lymphedema, and in certain instances we had been compelled to resort to amputation in order to relieve such patients of the pain and discomfort accompanying these conditions. The operation which Kondoleon has suggested is a safe and simple one, and it is to be hoped that it will stand the test of further usage and prove itself to be a means whereby we may successfully deal with these stubborn conditions.

Prior to 1908 operations in which the large arteries were ligated and others in which large amounts of edematous fat and hypertrophied skin were removed had been used but with poor success. In 1908 Handley suggested a method of operating for lymphedema of the arm secondary to cancer of the breast which he termed lymphangioplasty. His operation consisted in the placing, subcutaneously, from the wrist to the normal skin around the axilla and shoulder, of long strands of silk. This was done with an idea of having these strands act as setons to drain the fluids from the swollen arm into normal tissues. His preliminary report was encouraging, but later the operation was proved to be unsatisfactory and now is seldom used.
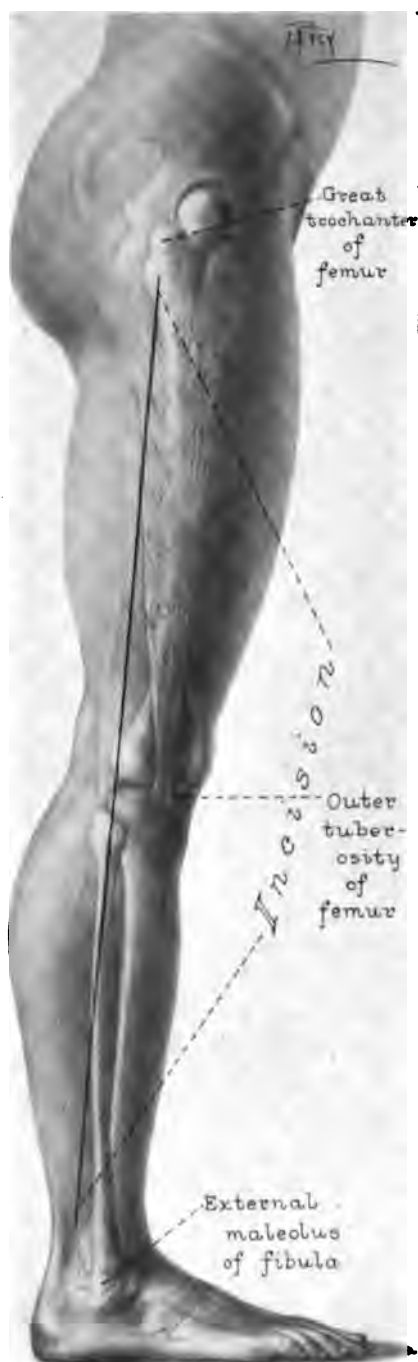
Fig. 307.—Line of incision on outer surface of the leg and thigh.
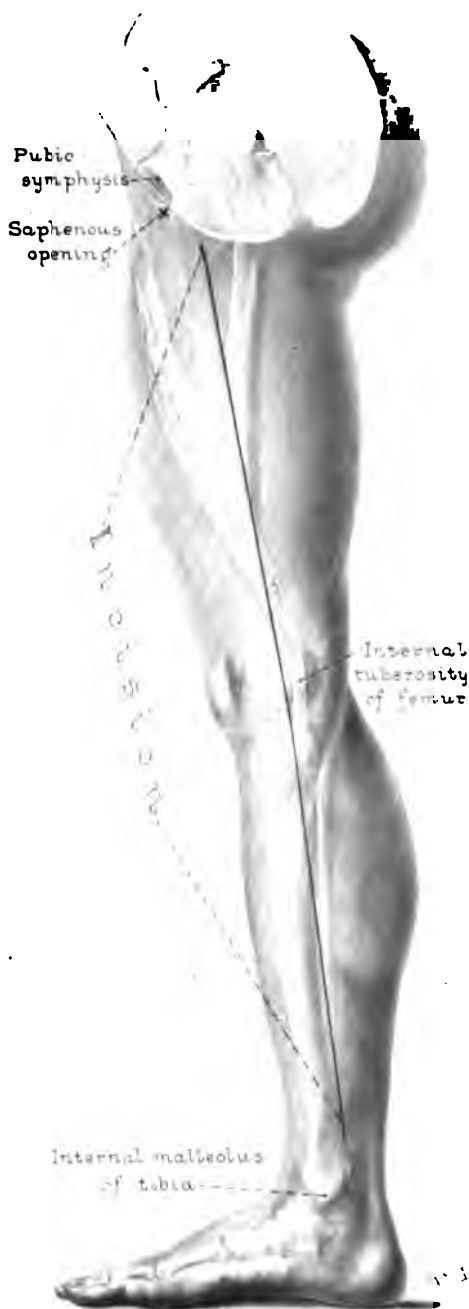
Fig. 308.—Line of incision on inner surface of the leg and thigh.

Lanz, in 1911, reported the result obtained by a new type of operation which he had performed on a patient suffering with idiopathic
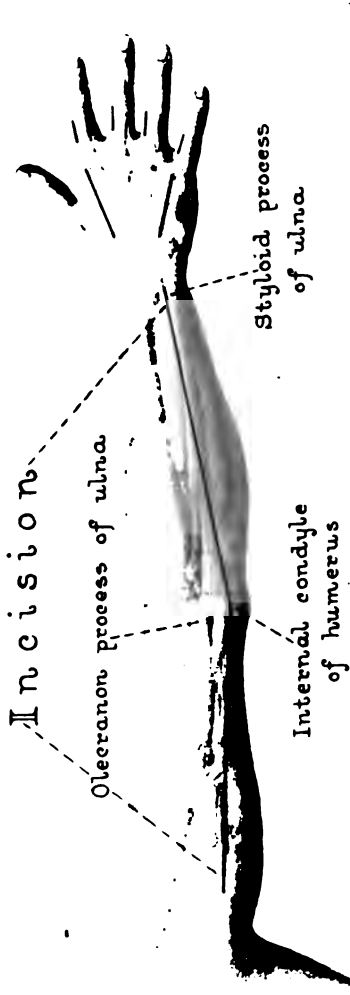
Fig. 309.—Line of incision on outer surface of the arm and forearm.
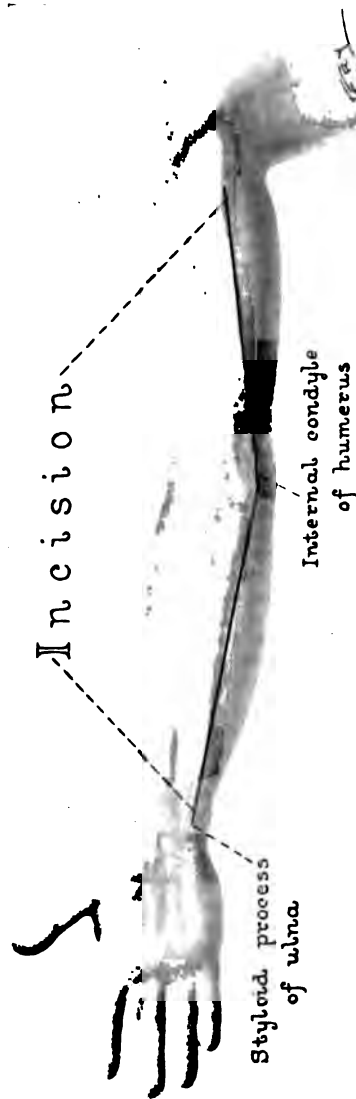
Fig. 310.—Line of incision on inner surface of the arm and forearm.

elephantiasis. His operation consisted in making a long incision in the thigh, exposing the femur, and trephining this bone at several points. Strips of fascia were then carried down through the muscles and inserted

into the openings previously made in the femur and the wound closed without drainage.

In 1912 Kondoleon, in a series of papers in which he gave credit to both Handley and Lanz for the work they had done in this connection, reported seven cases of lymphatic obstruction in which the patients had been operated on by the method now bearing his name. The operation was based on sound reasoning. He realized that the superficial and deep lymphatics were distinctly separated by the aponeurosis covering the muscles. His studies had shown that the edema in such patients was usually limited to the subcutaneous tissues and fat lying between the skin and aponeurosis. By removing portions of the aponeurosis he hoped to connect the superficial lymphatics with those of the deep group, and in this way obtain drainage of the superficial structures.

In the group of cases which he reported various types of lymphatic obstruction are to be found. Four of his patients had developed trouble following infections: one following the removal of the inguinal lymph-glands; another was a patient with idiopathic elephantiasis, and the last one a patient with an edema of the

Fig. 311.—Technic of Kondoleon operation. Aponeurosis has been incised, separated rom the muscle and sutured in such a way as to allow the subcutaneous fat to drop on the muscles after the wound has been closed. A portion of subcutaneous fat has been removed.

Segment of superficial fat excised

Ilio-tibial band of fascia lata

arm secondary to a carcinoma of the breast which had been removed and had later recurred in the axilla.   The results he obtained in this group of cases were uniformly good.
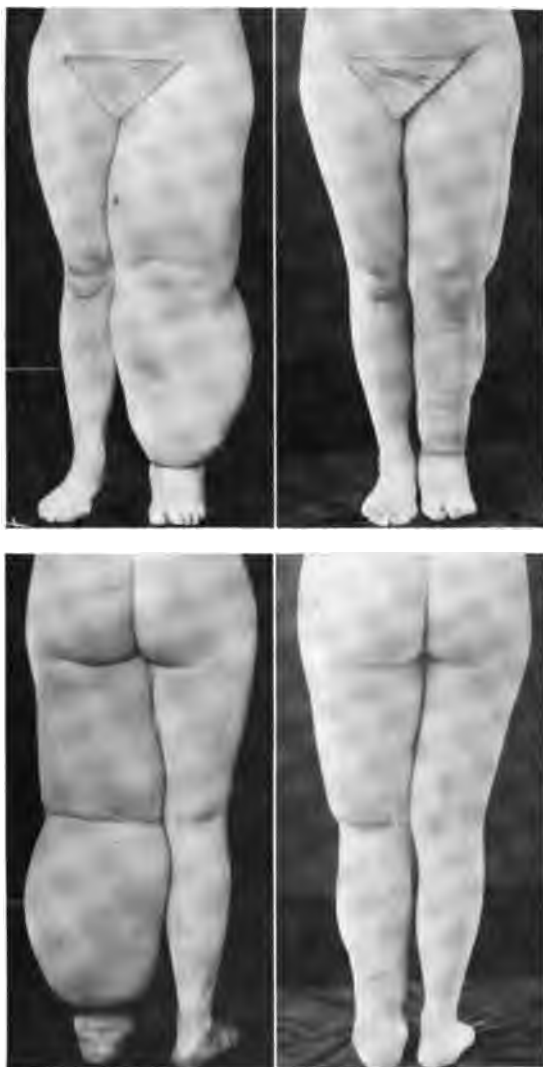
Fig. 312.—(41167.)   Anterior and posterior views before operation and three months after operation.

The technic of his operation is as follows: Long incisions are made along the inner and outer aspects of the affected limb, and through each

of these a large slice of edematous fat is removed. The aponeurosis is then opened, and a portion of it, three or four fingers in width, is excised. The wounds are closed without drainage in such a way that the skin with the fat attached to it comes in contact with the exposed muscles (Figs. 307–311).

I shall report herein three cases in which the operation was

Fig. 313.—(206558.) Views of the arm before operation and two and one-half months after operation.

done according to Kondoleon's method. Each of the operations was done in a different type of obstruction. In two enough time has not elapsed to show what the end result will be, but marked improvement has followed the operation in both cases.

CASE 41167.—A female, aged twenty-one years, with the congenital type of elephantiasis of the left leg which had been present since she was

one and a half years of age.   When first seen in the Mayo Clinic, the
patient was fifteen years old.   At that time there was a tremendous en-
largement of the left foot, leg, and thigh, and a marked thickening of the
skin covering these.   In August, 1911, according to Handley's method,
one silk strand was placed on the outer and one on the inner aspect of
the leg, from the ankle to the region of the left groin.   The patient re-
turned six months later without improvement—in fact, the enlargement
had increased.   In February, 1912, a double silk strand was placed sub-
cutaneously on the outer and inner aspects of the leg, and the inner of
these strands was extended upward into the fat of the abdominal
wall, while the outer strands were car-
ried as high as the left axillary line.
The condition remained unchanged until
her return more than four years later.
At this time—December, 1916—an op-
eration of the Kondoleon type was done,
first on the outer side of the leg and about
one month later on the inner side.   The
improvement was marked from the be-
ginning, and at the time of her discharge,
March, 1917, the leg was much smaller
than before the operation.   Letters re-
ceived since the patient returned home
indicate that the leg has continued to
diminish in size (Fig. 312).

CASE 170799.—A female, aged twenty
years, with elephantiasis nostras.   The
history was negative until she was eleven
years of age, when there was a severe in-
fection following vaccination on the left
arm.   After the vaccination wound
healed she was in good condition until
two years before coming to the Clinic.
At this time swelling of the left hand had

Fig. 314.—(170799.) Three months after
Kondoleon operation.   No operation was
done on the dorsal side of the hand and the
swelling has remained unchanged while the
arm has returned almost to normal.   Un-
fortunately, no photograph was taken in this
case before the operation.

developed and had slowly progressed until the forearm and arm were
involved in the process.   She had many attacks of erythema in the
swollen portion.   The history and findings in this case have been re-
ported in detail by Dr. Joseph A. Elliott.   At the time of our examina-
tion the patient presented a diffuse swelling of the arm, forearm, and
hand.   The swelling was more marked in the hand, and gradually di-
minished up to a point a few inches below the acromion process.   It also
involved the proximal phalanges of the fingers.   There was a definite
thickening of the skin.   July 13, 1917, an operation of the Kondoleon
type was performed, through incisions five or six inches long on the an-
terior and posterior surfaces of the arm and forearm.   No incisions were

made on the hand. Considerable improvement followed in the arm and forearm, but the condition in the hand remained stationary. Some swelling also remained about the elbow. A second operation was done September 29, 1917, at which time two incisions were made on the dorsal surface of the hand and one on each of the lateral surfaces of the elbow. Multiple incisions were also made on each proximal phalanx of the fingers. Although but a short time has elapsed since the last operation, the improvement has been quite noticeable (Fig. 314).

CASE 206558.—A female, aged fifty-one years, with lymphedema of the left arm following amputation of the breast with removal of the axillary glands. The wound had not been infected. Two months after the operation the arm began to swell, growing slowly but progressively worse and involving the dorsal surface of the hand, the forearm, and the arm nearly as high as the shoulder-joint. There was no thickening of the skin. September 1, 1917, a Kondoleon type of operation was done. Long incisions were made on the outer and inner aspects of the arm and forearm from a point a few inches below the shoulder-joint down to the wrist; also two incisions were made on the posterior surface of the hand. The swelling in the hand and arm decreased at once, and at present (two and a half months after the operation) they are almost normal in size. There has been also marked improvement in the forearm, but some swelling is still present. Should this persist, it is possible that further benefit might be derived through the excision of more of the aponeurosis (Fig. 313).

REFERENCES

1. Barber, R. S.: The Kondoleon operation. Surg., Gynec. and Obst., 1917, xxv, 104–105.
2. Elliott, J. A.: Elephantiasis nostras; review of the subject with report of a case. Jour. Cut. Dis., 1917, xxxv, 17–25.
3. Handley, W. S.: Lymphangioplasty: A new method for the relief of the brawny arm of breast-cancer and for similar conditions of lymphatic edema. Lancet, 1908, i, 783–785.
4. Hill, L. L.: Elephantiasis. Surg., Gynec. and Obst., 1915, xxi, 334–335.
5. Kondoleon, E.: Die operative Behandlung der elefantiastischen Oedeme. Centralbl. f. Chir., 1912, xxxix, 1022–1025.
   Die Lymphableitung als Heilmittel bei chronischen Oedemen nach Quetschung. Münch. med. Wchnschr., 1912, lix, 525–526.
   Die chirurgische Behandlung der elefantiastischen Oedeme durch eine neue Methode der Lymphableitung. München. med. Wchnschr., 1912, lix, 2726–2729.
6. Lanz: Eröffnung neuer Abfuhrwege bei Stauung in Bauch und unteren Extremitäten. Centralbl. f. Chir., 1911, xxxviii, 153–155.
7. Matas, R.: The surgical treatment of elephantiasis and elephantoid states dependent upon chronic obstruction of the lymphatic and venous channels. Am. Jour. Trop. Dis. and Prevent. Med., 1913, i, 60–85.
8. Moschowitz, A. V.: Lymphangioplastic for elephantiasis. Ann. Surg., 1915, lxii, 339.
9. Royster, H. A.: Elephantiasis and the Kondoleon operation. Jour. Am. Med. Assn., 1914, lxii, 1720–1722.
10. Shattuck, G. C.: Three cases of sporadic elephantiasis of the lymphatic type. Boston Med. and Surg. Jour., 1910, clxii, 107–111.

THE PREPARATION OF CYANAMID *

A. E. OSTERBERG AND E. C. KENDALL

———————

In the course of work undertaken in the chemical laboratory of the
Mayo Clinic it became necessary to prepare considerable quantities of
cyanamid in the free base form. The existing methods, particularly
those having as a starting-point thiourea[1] or calcium cyanamid,[2] were
tried and subsequently abandoned because of the tedious procedures and
poor yields obtained. Attempts were therefore made to modify the
method, using calcium cyanamid as a starting-point. The method of
treating calcium cyanamid with aluminum sulphate[3] was found to give
low yields because of the slight solubility of calcium cyanamid necessi-
tating many extractions of the starting material. In order to overcome
this objection calcium cyanamid was treated with dilute sulphuric acid.
This method, however, yielded variable results. Carbonic acid was
then tried in place of sulphuric. It was found unnecessary to dissolve
the calcium cyanamid in water before treatment. Simply allowing the
carbon dioxid to bubble through an aqueous suspension of calcium cyan-
amid results in its almost quantitative decomposition. A method by
which cyanamid may be easily obtained in a high state of purity is de-
scribed here in the hope that it may be of use to others.

The starting material was calcium cyanamid, furnished by the Baker
Chemical Company, having a total nitrogen content of 20 per cent.
The yield was 55 gm. of pure cyanamid per 200 gm. of the calcium salt.
This corresponds to a yield of 92 per cent of the theoretic.

Method.—200 gm. of calcium cyanamid were mixed in a three-liter
round-bottom flask with 1500 c.c. of distilled water. Into this mixture
CO_2 was passed until a neutral or only slightly alkaline point was reached,
as determined by red litmus. The flask was kept immersed in cold
water as the reaction causes a small rise in the temperature. We have
observed that if the temperature is kept below 40 C., there is very little

loss of the ether-soluble product due to polymerization to dicyandiamid. The length of time necessary to precipitate the calcium varies with the amount of agitation. We have found it convenient to allow the precipitation to proceed over night, agitating but little.

The precipitate was filtered on a Buchner funnel, well washed with water, and the filtrate placed in a three-liter round-bottom flask. A small amount of talcum was added to facilitate boiling and the solution was concentrated by distillation on a water-bath *in vacuo*. The distillation* was continued until the remaining solution, when cooled under the cold-water tap, formed a solid crystalline mass, which was then extracted three times with absolute ether. The ether was distilled off on a water-bath and the remaining solution concentrated over sulphuric acid *in vacuo*.

In this way 55 gm. of pure cyanamid were obtained in the form of deliquescent needles melting at 43 C. (when free from ether) and perfectly soluble in ether.

	Calculated for	Found
	CNNH$_2$	
N	66.67	67.00

REFERENCES

1. Volhard, J.: Jour. f. prakt. Chem., 1874, ix, 24.
2. Baumann, E.: Ver. Chem. Ges., 1873, vi, 1371.
3. Caro, N.: Ztschr. f. angew. Chem., 1910, xxiii, 2405–17; abstr. in Jour. Soc. Chem. Indust., London, 1911, xxx, 23.

* However, if a higher temperature than 40 C. is required to drive off the last traces of water it is best to stop at this point and remove the remaining water *in vacuo* over sulphuric acid after the ether extraction. This may lead to contamination of the resulting product with dicyandiamid, if any is present, as dicyandiamid is soluble in a cyanamid solution in ether. However, after drying, a second ether extraction will remove all dicyandiamid.

GENERAL

THE EFFECT OF TRAUMA ON THE LARYNGEAL NERVES

AN EXPERIMENTAL STUDY *

E. S. JUDD, G. B. NEW, AND F. C. MANN

From time to time a complete or partial paralysis of the vocal cords is seen following thyroidectomy. The purpose of this research was to determine, if possible, the cause of such paralysis. It was believed that the best method by which to attempt to solve the problem would be to study the effect of traumatic procedures on the recurrent laryngeal nerves in dogs.

The method of experimentation consisted in traumatizing the laryngeal nerves in a manner similar to that which could occur in an operation, and subsequently to study the function of the vocal cords. The results of these traumatic procedures can only be applied specifically to the recurrent laryngeal nerves, for the results may not be the same for other nerves of a different size or in a different location.

All operations were done under ether anesthesia, employing sterile technic. The various operations differed only in regard to the traumatic procedure used. On the day following the operation the function of the cords was observed. These observations were subsequently made as frequently and over as long a time as seemed necessary in each individual experiment.

The function of the vocal cords was observed by direct laryngoscopy without an anesthetic. It is impossible to get the animal voluntarily to approximate the cords, as may be done in the human being, but their action was readily observed when the dog attempted to make a noise. In observing complete bilateral cord paralysis in the dog, inspiration frequently causes approximation, but this is easily differentiated from a functionating cord. To make the observation free from all personal bias the observer made notes of the result of his examination without

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knowledge of the operation performed or the results of his previous observations.

Injury to the recurrent laryngeal nerves produces some general effects which should be noted. The severity of these effects depends on whether one or both nerves are injured and also the anatomic site of injury. Owing to the fact that the laryngeal nerve gives off branches to the trachea and esophagus, the results of injury are greater when these branches are also involved, that is, when the point of injury is at a considerable distance from the larynx.   Usually when only one nerve is involved, the general results are not marked.

Complete destruction of the function of both recurrent laryngeal nerves at a point below the lower poles of the thyroid of the dog results in some inability of the animal to swallow properly, a total loss of voice, and sometimes dyspnea.   In most cases very little effect on the ability of the animal to swallow was noted.   The voice was always lost, although in many instances the animal was able to produce various sounds. Many of the animals suffered from dyspnea continuously, while most of the others could be made dyspneic from exertion.   This result, which differs from that observed in man, is probably due to the fact that the paralyzed cords tend to fall inward on inspiration in the dog and to form pockets laterally.   This acts like a valve, and in extreme cases the air will be completely shut off.   The faster and harder the animal attempts to breathe, the greater the difficulty of passing air into the trachea.   Many of the dogs could not exert themselves in the least without inducing the greatest dyspnea and in some cases cyanosis.

The effect of pinching was studied.   The nerves were picked up at various points of their course and pinched once with a hemostat in a manner similar to that necessary to stop hemorrhage from a small vessel.   In every instance in which a nerve was pinched the corresponding vocal cord was paralyzed.   In all animals that lived long enough the function of the cord was later fully restored.   The time necessary for the restoration of the function depended on the anatomic point at which the nerve was pinched.   When the trauma was applied to the nerve at its entrance into the larynx, the function of the cord was found to be restored as early as thirty days after operation; when the nerve was pinched below the lower pole of the thyroid, sixty days elapsed before the cord functionated normally.

Three kinds of suture material were used to study the effect of ligation, linen, chromic catgut Nos. 1 and 2, and plain catgut No. 1.   The

nerves were ligated with about the same tension used in ligating small vessels. Every cord, where the nerve was ligated, was paralyzed, and in no instance was recovery noted, although in the majority of experiments the observations were carried on long enough for regeneration to have occurred. It seems that all suture material produces enough permanent obstruction to prevent regeneration in a nerve as small as the laryngeal. At necropsy this obstruction, due to the suture material or the reaction to it, could be definitely located grossly.

Several of the nerves were sectioned and allowed to drop back into their original position. The cords paralyzed by the procedure never recovered. Some of these nerves were examined at necropsy, and the ends were found to be as far apart as 0.5 cm.

Three methods were employed to stretch the nerves. In some instances a hemostat was placed under both nerves, and traction was applied for a definite length of time, which varied from ten to thirty minutes. In other experiments small retractors were placed on each side, below the lower pole of the thyroid, and traction outward was made for a definite length of time. In the latter case the nerve itself was not disturbed. Finally the nerve was dissected free for a considerable length, and after splitting one of the muscles of the neck, the nerve was sutured around it in such a manner as to place it on tension. In all instances the stretching was more severe than would occur during operation, and by the first two methods produced paralysis in only one case. It is possible that this was due to trauma at the time of exposure and not to the stretching. When the nerves were stretched over muscles, paralysis occurred more frequently, but this also was due probably to the operative trauma and not to the stretching.

In several animals the nerves were dissected free for several centimeters (explored). In some cases paralysis followed, probably due to the trauma incident to freeing the nerves.

In four experiments the superior laryngeal nerves were sectioned. Subsequent examination of the vocal cords did not reveal any impairment of function.

The table gives the data in an abbreviated form. Many of the experiments were ended prematurely because of an epidemic of distemper.

TABLE SHOWING THE RESULTS OF EXPERIMENTS ON THE EFFECT OF TRAUMATIC PROCEDURES TO THE RECURRENT LARYNGEAL NERVES

EXPERI-MENT	OPERATION (PINCHED)	RESULTS
494–16	Pinched right nerve	Complete paralysis. No restoration of function at the end of 17 days
500–16	Pinched both nerves	Complete paralysis. Function of left cord restored within 40 days; function of right cord normal within 63 days
511–16	Pinched right nerve	Complete paralysis. No restoration of function on fourth day
512–16	Pinched right nerve	Complete paralysis. No restoration of function within 15 days
598–16	Pinched both nerves	Complete paralysis. No restoration of function within 10 days
599–16	Pinched both nerves	Complete paralysis. Function fully restored within 50 days
600–16	Pinched both nerves	Complete paralysis. Function fully restored 50 days after operation
611–16	Pinched left nerve	Complete paralysis. Function fully restored 48 days after operation
651–16	Pinched left nerve at level of lower pole of thyroid. Pinched right nerve 5 cm. below point at which left was pinched	Complete paralysis. Function of left cord restored 49 days after operation; right was still slightly paralyzed. It completely regenerated later
654–16	Pinched right nerve	Complete paralysis. No restoration of function at end of twenty-second day
663–16	Pinched right nerve	Complete paralysis. No restoration of function within 18 days
664–16	Pinched both nerves near lower pole of thyroid	Complete paralysis. Function restored within 45 days
738–16	Pinched right nerve below level of lower pole of thyroid; pinched left nerve just below point of entrance into larynx	Complete paralysis. Function of right cord not restored within 26 days; function of left about half restored
739–16	Pinched both nerves at entrance to larynx	Complete paralysis. Twenty-sixth day right cord paralyzed 2; left cord paralyzed 1; thirtieth day right cord paralyzed 1; left cord normal; thirty-third day right cord normal
740–16	Pinched right nerve	Complete paralysis. No restoration of function within 24 days
741–16	Pinched both nerves	Complete paralysis. No restoration of function within 25 days

EXPERI-MENT	OPERATION (LIGATED WITH PLAIN CATGUT)	RESULTS
601–16	Ligated both nerves	Complete paralysis. Left cord removed ninth day for marked dyspnea. No regeneration of right nerve within 320 days
742–16	Ligated both nerves	Complete paralysis. No restoration of function within 22 days
12–17	Ligated both nerves	Complete paralysis. No restoration of function within 228 days

TABLE SHOWING THE RESULTS OF EXPERIMENTS ON THE EFFECT OF TRAUMATIC PRO-
CEDURES TO THE RECURRENT LARYNGEAL NERVES—(*Continued*)

EXPERI-MENT	OPERATION (LIGATED WITH CHROMIC CATGUT)	RESULTS
503–16	Ligated right nerve	Complete paralysis. No restoration of function within 75 days
504–16	Ligated both nerves	Complete paralysis. No restoration of function within 46 days
505–16	Ligated right nerve	Complete paralysis. No restoration of function within 318 days
506–16	Ligated right nerve	Complete paralysis. No restoration of function within 371 days
611–16	Ligated right nerve	Complete paralysis. No restoration of function within 22 days
613–16	Ligated right nerve	Complete paralysis. No restoration of function within 110 days
665–16	Ligated right nerve	Complete paralysis. No restoration of function within 18 days

EXPERI-MENT	OPERATION (LIGATED WITH LINEN)	RESULTS
499–16	Ligated both nerves	Complete paralysis. No restoration of function within 16 days
502–16	Ligated right nerve	Complete paralysis. No restoration of function within 372 days
503–16	Ligated left nerve	Complete paralysis. No restoration of function within 75 days
665–16	Ligated left nerve	Complete paralysis. No restoration of function within 18 days

EXPERI-MENT	OPERATION (SECTIONED)	RESULTS
493–16	Sectioned right nerve	Complete paralysis. No restoration of function within 237 days
509–16	Sectioned right nerve	Complete paralysis. No restoration of function within 262 days
510–16	Sectioned left nerve	Complete paralysis. No restoration of function within 15 days
511–16	Sectioned left nerve	Complete paralysis. No restoration of function within 11 days
512–16	Sectioned left nerve	Complete paralysis. No restoration of function within 22 days
655–16	Sectioned left nerve	Complete paralysis. No restoration of function within 90 days
10–17	Sectioned right nerve	Complete paralysis. No restoration of function within 7 days

EXPERI-MENT	OPERATION (RESECTED)	RESULTS
493–16	Resected 5 cm. of left nerve	Complete paralysis. No restoration of function within 237 days

TABLE SHOWING THE RESULTS OF EXPERIMENTS ON THE EFFECT OF TRAUMATIC PRO-
CEDURES TO THE RECURRENT LARYNGEAL NERVES—(*Continued*)

EXPERI-MENT	OPERATION (STRETCHED FOR PERIOD OF OPERATION)	RESULTS
508–16	Stretched both nerves for short interval, probably two minutes	Cords normal
509–16	Stretched left nerve	Cord normal
656–16	Stretched both nerves for ten minutes	Cords normal
666–16	Stretched both nerves for twenty minutes	Left cord paralyzed 3. Right cord normal. Both cords normal within 18 days
13–17	Stretched both nerves for twenty minutes	Cords normal

EXPERI-MENT	OPERATION (STRETCHED BY SUTURING AROUND MUSCLES)	RESULTS
653–16	Sutured both nerves around muscles	Complete paralysis. Function restored within 218 days
651–16	Sutured left nerve around muscles	Complete paralysis. No restoration of function within 22 days
655–16	Sutured right nerve around muscles	Cord normal

EXPERI-MENT	OPERATION (EXPLORED)	RESULTS
502–16	Explored left nerves	Cord normal
510–16	Explored right nerve	Complete paralysis. Did not recover within 15 days
665–16	Explored left nerve	Complete paralysis. Did not recover within 18 days
9–17	Explored both nerves	Complete paralysis. After 6 days left cord paralyzed 2; right cord complete; after 10 days left 1, right 3; after 14 days left O. K., right 3; after 23 days right 2. Both cords normal on eighty-ninth day
10–17	Explored left nerve	Cord normal
11–17	Explored both nerves	Left cord normal; right paralyzed; bloody effusion from wound; much bleeding on right side at operation. Right cord still paralyzed after 20 days

CONCLUSIONS

1. Section of the recurrent laryngeal nerve produces complete paralysis of the vocal cord of the corresponding side, which in all probability will be permanent.

2. Ligation of the recurrent laryngeal nerve with linen, chromic catgut, or plain catgut produces complete and probably permanent paralysis of the vocal cord of the corresponding side.

3. Stretching the recurrent laryngeal nerves acutely in a manner similar but of longer duration and intensity than occurs in operation does not impair the function of the vocal cord.

4. Stretching the recurrent laryngeal nerves for a long period, as over muscles, impairs the function of the vocal cords, but the impairment is probably due to the operative trauma and not to the stretching.

5. Pinching the recurrent laryngeal nerves with a hemostat in a manner similar to that which may occur in an operation produces temporary paralysis of the vocal cords. Restoration of function always occurs, the length of time necessary for restoration depending on the anatomic point at which the nerve was crushed. The time found necessary for complete regeneration of the nerve when injured in the areas usually traumatized by operation varies between thirty and sixty days.

6. Exploration of the recurrent laryngeal nerves produces an effect on the vocal cords depending on the amount of trauma to which the nerves are subjected. Careful dissection will probably not produce any effect; the paralyses noted were probably owing to pinching and other traumatic procedures.

Pinching: Number of nerves pinched, 24. All cords were paralyzed. The function of all the cords in which the nerves were pinched at the lower pole of the thyroid was restored within sixty days. When the nerves were pinched close to the larynx, the function of the cords was found to be restored within thirty days.

Ligation with chromic catgut: Number of nerves ligated, 9. All cords were paralyzed. The function was never restored. Longest time observed after operation was 371 days.

Ligation with plain catgut: Number of nerves ligated, 6. All cords were paralyzed. The function was never restored. Longest time observed after operation was 320 days.

Ligation with linen: Number of nerves ligated, 4. All cords were paralyzed. The function was never restored. Longest time observed after operation was 372 days.

Section: Number of nerves sectioned, 8. All cords were paralyzed. The function was never restored. Longest time observed after operation was 372 days.

Resection: Number of nerves resected, 1. The cord was paralyzed. The function was not restored after 160 days.

Stretched (acute): Number of nerves stretched, 9. In one case the cord was paralyzed. No paralysis occurred in eight cases.

Stretched over muscles: Number of nerves used, 4. Three cords were paralyzed. The function of two was restored within forty-eight days; the third was still paralyzed on twenty-second day.

Explored: Number of nerves explored, 8. Three were not paralyzed; three were paralyzed and remained so at the end of fifteen, eighteen, and nineteen days respectively. The function of one was restored in fourteen days; the function of another was partially restored after twenty-three days.

ANGIOMA AND RADIUM*

G. B. NEW

The specific action of radium on vascular tissues has been known since it was first used for therapeutic purposes. Striking results from this treatment of angioma have been reported in the literature both in this country and in France. Small quantities of radium used in the treatment of superficial angiomas or purplish birthmarks bleach out the condition, and leave the skin almost normal in appearance. But in the treatment of this type of lesions extreme care is required, or a whitish, disfiguring scar is produced. Such superficial conditions are best treated by a small plaque of radium kept constantly moving over the involved area, so that the effect of the radium will be distributed evenly over it.

Large cavernous angiomas often seen about the face and scalp in children require larger quantities of radium. It may be used in the form of a plaque or tube properly screened and elevated from the tumor. When emanations are available, they may be employed. A preferable method of treating such conditions, however, is to place a tube of radium in a rubber finger-cot, and insert it directly into the tumor. In using this method in cavernous angiomas about the lips and cheeks in children ether anesthesia should be given. A small incision is then made inside the mouth a short distance from the angioma, and the radium inserted directly into the tumor through a channel burrowed with a small straight forceps. The incision is closed with catgut. When the work is done entirely on the inside of the mouth, there is no visible scarring and no deformity of the skin. The tumor disappears, leaving a normal condition. In young children, particularly, such a method is preferable, as the radium is placed where it is needed, and kept there the necessary length of time. It is well to wait two or three months between treatments so that the full value of the radium may be seen before

further treatments are given.   Angiomas, in young children particularly, respond readily, but many remarkable results are seen in adults.

Fig. 315.—(111960.) Cavernous and superficial angioma of the cheek   Fig. 316.—(111960.) Same as Fig. 315, six months after treatment.

Extensive cavernous angiomas about the tongue and the floor of the mouth, involving the submental and submaxillary regions, are best treated by the cross-firing method from the inside of the mouth and the

outside of the neck. In this way many conditions that are hopeless from a surgical standpoint are cleared up.

Fig. 317.—(118722.) Extensive cavernous angioma of the left cheek, involving the nose, inner canthus, and upper lip. Scarring from previous operations.

Fig. 318.—(118722.) After treatment with radium, scarring the result of previous operations.

The following cases are illustrations of the use of radium in angiomas:

CASE 1 (111960).—H. A. C., a child aged five months, was brought to the Clinic August 3, 1914, because of an angioma on the right side of

the face. The tumor was noticed at birth, but its color had deepened, and it had grown larger; otherwise the child appeared to be quite normal. Two treatments with the electric needle had been given six weeks previously. The right side of the face, extending from above the right brow and including the entire right cheek, was larger than the left

Fig. 320.—(150124.) Same as Fig. 319, seven months after one treatment with radium.

Fig. 319.—(150124.) Cavernous angioma of the upper lip and the nose.

and appeared swollen. On the right cheek was a dark-purplish superficial angioma (Fig. 315). Five deep injections of hot water at intervals of six weeks to three months were given for the cavernous angioma. A 5-mg. plaque of radium covered with a finger-cot was applied over the entire area of the superficial angioma two different times, for six and six

and one-half hours, respectively, with an interval of three months between treatments. The second photograph (Fig. 316) was taken

Fig. 322.—(176169.) After treatment with radium.

Fig. 321.—(176169.) Cavernous angioma of the upper lip and the nose. Child also has marked eczema.

February 14, 1915, six months after the beginning of the treatment. The cavernous part of the angioma had entirely disappeared, as had also the superficial angioma. While in this case hot-water injections

were given for the cavernous part of the condition, we have found in a series of cases that radium gives much better results. Fewer treatments are required, and they are less painful.

Fig. 324.—(176169.) Same as Fig. 323 (after treatment).

Fig. 323.—(176169.) Same as Fig. 321 (side view).

CASE 2 (118722).—K. F., a child aged nine months, with a tumor of the left cheek, which bulged to the side of the nose and upper lip, was

examined in the Clinic November 11, 1914. The tumor was noticed one week after birth. Five operations from the outside of the cheek had been done in attempts to reduce the tumor, without success. The tumor continued to grow larger. The first operation was done when the child was eleven weeks old. Examination showed a large cavernous angioma of the left cheek, which was much scarred from the operations (Fig. 317). Four radium treatments were given between April 1, 1915, and August 4, 1916, a 25-mg. tube of radium in a finger-cot being inserted directly into the tumor in four different locations over the face. In addition, a 5-mg. plaque of radium screened with a finger-cot was used in two treatments. It was kept moving over the tumor, one time for four hours and the other time for eight hours. The photograph (Fig. 318), taken March 29, 1917, shows the result of the treatments. The scarring on the outside of the cheek is due to five operations. This scarring is now being treated.

CASE 3 (150124).—L. S., a child aged four and one-half months, with a large cavernous angioma involving the entire upper lip and the lower part of the nose, was examined in the Clinic January 18, 1916. The growth was noticed three or four days after birth, but it had gradually increased in size. The child had not been treated. There was superficial ulceration and crusting on the center of the lip (Fig. 319). January 21, 1916, a 25-mg. tube of radium in a rubber finger-cot was inserted into the tumor of the upper lip from the inside, and left in place twelve hours. The child was not seen again until August 26, 1916, seven months later. The condition at that time is shown in Fig. 320.

CASE 4 (176169).—J. S., a child aged four months, was brought to the Clinic October 24, 1916, because of angioma of the upper lip. The tumor was noticed at birth, and had been increasing in size. It had been treated by injections of alcohol once a week for six consecutive weeks with no improvement. The examination showed a large cavernous angioma involving the entire length of the upper lip, and bulging the lower part of the nose. The lip was one inch thick in the center. There was also a marked eczema on the face and scalp (Figs. 321 and 322). October 26, 1916, a 25-mg. tube of radium in a rubber finger-cot was inserted into the inside of the upper lip, and left in place eight hours. The child was brought back February 1, 1917, with the lip 75 per cent better than when first examined. A 22-mg. tube of radium was again inserted into the inside of the lip, and left in place for eight hours. When next examined, April 10, 1917, the lip was quite normal (Figs. 323 and 324).

The use of radium in the treatment of angioma is especially gratifying since surgical measures are of little value. The condition usually recurs following any operative procedure, and the scarring that results is disfiguring (Fig. 318). In my experience angiomas have not recurred following their removal with radium.

SHOCK DURING GENERAL ANESTHESIA*

F. C. MANN

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Owing to the indiscriminate use of the term "shock," it seems necessary to define the meaning of the word as applied to this particular discussion.[1] It is used in the sense that the surgeon applies it when a patient develops alarming symptoms during or immediately following an operation, the definite cause of which is doubtful. While the data and conclusions presented are, to a considerable extent, experimental in origin, they may also be applied to corresponding clinical conditions. The two points of paramount importance in considering the subject of shock during general anesthesia are the cause or the causes of the condition and the effect of the anesthetic in either preventing or accentuating it. Owing to the general use of ether and the ease with which definite tensions may be administered, it was the only anesthetic used in my experiments, and all the conclusions are based on this anesthetic.

In the history[2] of the subject there has always been a tendency to ascribe the condition of shock to a single cause, although the condition itself and the circumstances under which it developed have been quite varied. This tendency in all probability has reached its zenith and it is quite probable that in the future both experimental observers and clinicians will study the subject with the view to determine the cause in each individual case. It is my purpose to discuss here the different possible causes of shock during anesthesia, the probable physiologic mechanism involved, and their relation to ether anesthesia.

In general, surgeons agree that the most common cause of the symptoms of shock, either as a primary or a secondary factor, is free hemorrhage. Experimentally this has also been found to be true. Many investigators have carefully determined and reported on the mechanism involved. It is important to emphasize the points that all persons do

not react the same to identical losses of blood, and that estimates of the
amount of blood lost during operative procedures must be inaccurate.
Further insight into this form of shock awaits our more complete knowl-
edge of the control of the volume of blood.   It should be noted that the
reaction following hemorrhage is very similar, particularly in regard to
the vasomotor mechanism, to that following trauma to the abdominal
viscera.[3]

The only uniform and certain method of producing shock experimen-
tally is by exposure of the abdominal viscera.   The time necessary to
expose the viscera before shock develops is variable, depending on many
conditions.   Usually a state of deep shock takes place within an hour
or two.   Owing to the fact that in most experimental work shock has
been produced by exposure of the abdominal viscera and that clinically
most cases of postoperative shock develop after abdominal operations,
more is known concerning this form of shock than any other.   While
the mechanism which produced the condition is not fully understood,
many of the most important factors are known.

Undoubtedly the cause of shock produced by exposure and trauma
of the abdominal viscera is mainly due to a failure of the venopressor
mechanism, as enunciated by Henderson,[4] although in all probability
loss of carbon dioxid is not the primary factor. · The investigations of
Janeway and Ewing,[5] my own experiments, and the work of others[6]
make it possible to follow quite clearly the process by means of which
the condition of shock is produced when the viscera are exposed.   The
process is as follows:

When the great delicate vascular area of the viscera is first exposed
to the air, changes of temperature, and handling, there is an immediate
dilatation of all the arterioles in the exposed area.   Rarely a short
period of constriction precedes the dilatation.   As a result of this dilata-
tion of the splanchnic arterioles, blood-pressure decreases.   The splanch-
nic capillaries and veins are markedly distended, which may be due to
one or all of the following causes: a local inhibition of vasomotor tone,
an active dilatation, changes in abdominal pressure, and venous ob-
struction.   On the whole, the process resembles the first stage of acute
inflammation and does not appear to differ essentially from the phenom-
ena as observed in the classic experiments on the subject.   After this
initial fall in blood-pressure the condition of the animal may remain
stationary or may even slightly improve.   However, as the loss of tone
and paralysis of all the tissue involved take place, the blood-pressure pro-

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gressively falls, the temperature becomes subnormal, and the animal develops profound shock. This loss of circulatory fluid and changes in temperature quickly imperil the life of the cells of the rest of the organism and death usually results from anemia of the medullary centers, particularly the respiratory. At the time the viscera are exposed and during the period that shock is developing, the vasomotor center increases in tone and the untraumatized arteries constrict. The amount of this constriction depends on their previous condition and the degree of splanchnic dilatation. During this time the center will usually respond to reflex stimulation and asphyxia, which demonstrates that it is still active although not functionating to its maximum extent. When the state of shock is fully developed it is usually, but not always, possible to obtain a response of the center, due to the long-continued blood-pressure or to the fact that all untraumatized arteries are constricted to their maximum extent or that the great splanchnic area, through which most reflex responses of blood-pressure are produced, is completely paralyzed.

The heart and respiratory mechanism are probably affected mainly by the loss of circulating fluid. The following facts should be emphasized: That the resulting condition is essentially one of loss of circulating fluid; that the process takes place in the area traumatized and in that sense it is peripheral; that the primary involvement of the nervous system is probably mainly in regard to the local reflexes; and that the higher nervous mechanism is affected secondarily.

I have never been able to produce in an etherized animal the shock produced by excessive nervous irritation which is the most popular clinical cause of the condition. A careful review of experimental work leads me to believe that other investigators have experienced the same difficulty. While all traumatic procedures, such as crushing joints, evulsing nerves, etc., will produce marked respiratory and blood-pressure changes, it must be very rare for the condition of shock to develop. This must be due either to the fact that nerve impulses are not the primary factors in the cause of shock, or that ether protects the nervous mechanism from excessive stimulation.

The phenomena of so-called psychic shock, the shock of railway and other painful accidents, all testify that at least in some instances the nervous mechanism may be a factor in some forms of shock. An explanation of the cause of the condition in these cases is most difficult.

I have studied recently the effect of different traumatic procedures

on decerebrated animals. Exposure of the abdominal viscera produces the condition of shock in exactly a similar manner in a decerebrated animal as in an etherized animal. No difference in the development of the process could be noted. Traumatic procedures on the limbs and nerves of a decerebrated animal, while producing marked individual variations, produce greater changes in respiration and blood-pressure than in etherized animals, and in a very small percentage of instances death is actually produced. This condition probably corresponds to the shock produced by accidents; I am not sure it has any relation to the shock produced under an anesthetic.

In the few instances in which death occurred, I was unable to determine the cause. However, I believe the factors involved will be found to be either excessive inhibition, as held by Meltzer,[2] a decrease in general tone due to changes in the synapses, as suggested by Hill,[7] or excessive depressor stimulations. If the latter is true, work along the line pursued by Ranson[8] should give positive results.

It is highly improbable that physiologic fatigue will be found to play any primary part in the production of shock, or at the most in only a small percentage of instances. The belief that physiologic fatigue is not a common cause of shock during anesthesia is based on several facts. The work of Porter,[9] which demonstrated that the vasomotor center is not primarily fatigued by excessive stimulation and that electrical stimulation of the major nerve-trunks for many hours did not produce shock, and my own experiments,[10] which show that it must be rare indeed for shock to be produced in an etherized animal by excessive trauma to nerves and limbs, prove that from the experimental standpoint fatigue is not of great importance.

In a recent series of experiments I have investigated, quantitatively, the relation of nerve impulse to shock. Utilizing the method devised by Forbes and Miller[11] to detect the changes in potential at the brainstem of decerebrated animals following nerve stimulation, I have attempted to determine quantitatively the amount of nerve reaction produced by various operative procedures.

The method, which did not differ from that described by Forbes and Miller except that the electrodes were made large enough to connect both sides of the brain-stem, consisted of connecting the brain-stem of a decerebrated cat to a galvanometer and recording the changes in potential produced by different traumatic and operative procedures. These

changes in potential depend on nerve reaction and have been shown to be a true index of the nerve impulse.[12]

Many difficulties were encountered in the investigation, the most important of which was to obviate the mechanical factor. Very slight movements of the brain-stem will produce deflections of the galvanometer. This error was never fully obviated. However, by carefully immobilizing the animal and making careful controls it was possible to determine some of the effects of traumatic procedures. Of course, only comparative studies could be made.

The results of this investigation are difficult to interpret, and until more experiments are performed conclusions must be cautiously made. However, the following facts seem true: (1) Traumatic and operative procedures on the limbs, joints, and nerves produce a very marked nerve response, as shown by the deflection of the galvanometer; (2) exposure of the abdominal viscera produces either no deflection or a very slight one; and (3) pulling on the mesentery and other viscera produces a definite deflection but not so great as that usually produced by trauma to a leg. In fact, it was possible to expose the viscera and cause shock in an animal without producing any deflection of the galvanometer.

If future experiments, in which all errors are eliminated, prove these results to be absolutely true, it will be justifiable to conclude that the nerve impulse bears no qualitative relation to shock. The idea that shock due to visceral trauma is not dependent on a primary impairment of the higher nerve mechanism will be substantiated.

In the experience of some surgeons a small number of cases have occurred in which the amputation of a limb, an operation for an ununited fracture, or similar operations have resulted in conditions of shock. The experimental investigator has never been able to explain the cause of shock in these cases because he has not been able to reproduce them. The recent work of Bissell[13] and of Porter[14] will probably clear up these obscure cases. Bissell has shown that in patients suffering from fractures of the long bones there is a great increase in the fat content of the blood. Some of the patients dying with symptoms of surgical shock following operation which involved considerable trauma to large areas of fat showed a large amount of fat in the lungs, death being due undoubtedly to pulmonary fat embolism. Porter, while studying shell shock, was led to consider the possibility that fat embolism was the cause of the low blood-pressure found in cases in which fractures had occurred. Undoubtedly in a small percentage of cases in which hitherto

a diagnosis of surgical shock has been made it will be found that the patients are suffering from pulmonary fat embolism.

The endocrine glands have been given as factors in the etiology of shock. This idea has been largely associated with the suprarenals and is based on the facts obtained as follows: Elliott[15] showed that stimulation of an afferent nerve produced a discharge of epinephrin; Cannon and De La Paz[16] demonstrated that there was a discharge of epinephrin during emotional states; Corbett[17] investigated the epinephrin content in shocked animals and found it greatly diminished. Bedford and Jackson[18] found that in conditions of low blood-pressure there was an increased amount of epinephrin in the blood. Bedford[19] showed that it was an active secretion of the suprarenals. Stewart and Rogoff[20] concluded, from their work on the effect of nerve and drug stimulation on the suprarenal, that the discharge of epinephrin from the suprarenal is not indispensable to life or health. My own experiments[21] have demonstrated that an animal may live for several days after the removal of all suprarenal tissue and maintain an apparently normal condition in all respects, including emotional reactions, and that an animal will survive and be maintained normally with only one-half to one-third of one suprarenal which has been separated from all nerve supply.

In all probability some of the endocrine glands, particularly the suprarenals, enter as factors into the complex condition of shock, but it is quite difficult to determine to what degree they participate as primary active agents in producing the state or how much they are affected by the low blood-pressure and the changes incident to the condition itself.

There is no doubt that an anesthetic may prove harmful to a patient, but it is not possible to state to what degree ether is a factor in the production of shock. Henderson[4] has pointed out the dangers of light anesthesia. Certainly an animal can be killed in the very early stages of etherization by a too high concentration administered during excessive respiration, but this is more of an anesthetic than a shock problem. The effect of trauma and nerve stimulation during very light etherization probably causes harmful results mainly because of the ensuing struggling which they produce, as was shown by Gatch, Gann, and Mann,[22] than for any other cause.

There seem to be little definite data as regards the question of whether hemorrhage under an anesthetic affects the individual more than without the anesthetic. My own experiments are too few at present to allow conclusions to be drawn. Also it has not been deter-

mined to what extent the loss of blood changes the reaction to definite tension of ether. Boothby[23] cites a case in which it was necessary to maintain the anesthetic tension the same as it was before (47) after a severe hemorrhage.

The result of excessively deep etherization is more nearly related to shock. Animals may be anesthetized for nine to ten hours with an ether tension just sufficient to maintain anesthesia for operative work without the production of a condition resembling shock. On the other hand, a higher tension which will depress blood-pressure to or below the critical level if maintained for one hour will produce most of the symptoms of shock. In such instances the blood-pressure usually remains low and is not restored after an hour or two of artificial respiration. The animal depressed by ether, however, differs from the animal in shock in the fact that the former will become conscious and require more anesthetic even with a low blood-pressure, while the latter usually will not. This depressed condition following deep etherization, while it is primarily due to the ether, is soon complicated by the condition itself, namely, low blood-pressure, subnormal temperature, etc. The shock-like condition resulting is quite largely due to these secondary factors.

While ether depresses the vasomotor center directly, it should be noted that the vascular system is affected by deep etherization in many other ways. Gatch[24] has pointed out that deep etherization also affects blood-pressure by loss of muscular tone and a decrease in the action of the respiratory pump.

While studying the vascular and respiratory reflexes under various tensions of ether, I observed one phenomenon which may have a direct bearing on the cause of some cases which were diagnosed as shock. Stimulation of the vagus nerve and most of the other mixed nerves by a suitable electric stimulus will produce inhibition of respiration. Simple stretching of some nerves, particularly the brachial plexus, will sometimes stop respiratory movements. It is interesting to note that ether never blocks these inhibitory reflexes, but as long as the respiratory center acts the reflexes are present. As the respiratory mechanism is depressed by the higher tensions of ether, the inhibition following nerve stimulation usually becomes more pronounced. Finally, it is possible to use a tension under which respiration, though greatly depressed, would afford enough ventilation to keep the animal alive but which would be inhibited for so long following nerve stimulation that the animal would in all probability die if artificial respiration were not

maintained. This combination of deep anesthesia with inhibition of respiration may have been a factor in some cases which were called shock.

Bernstein[25] seems to have been the first to investigate the place in the reflex arc on which the general anesthetics (chloroform) acted. By destroying the blood supply to a portion of the spinal cord of an animal so that certain segments would not be affected by the anesthesia, he showed that stimulation of a sensory nerve whose cell-body was in an anesthetized part would not produce a motor response, but that the stimulation of a sensory nerve whose cell-body was not anesthetized would produce a motor response. This proved that chloroform acted first on the sensory side of the reflex arc. Deeper anesthetization depressed the motor side as well.

In a previous investigation of the condition of shock I concluded that ether prevented afferent impulses from reaching the higher nerve centers. Recently Forbes and Miller,[11] by means of the galvanometric method previously described, have clearly demonstrated this fact in a very delicate and graphic manner. By connecting a galvanometer to the brain-stem of a decerebrated cat they were able to show that a weak stimulation of the sciatic nerve produced a deflection of the galvanometer corresponding to a difference of the potential following nerve response; after etherization this deflection did not occur, but reappeared when the animal recovered from the anesthetic. Undoubtedly ether does block afferent nerve impulses to the higher centers.

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SUMMARY

Surgical shock, using the term in the sense employed by the surgeon, occurring during general anesthesia may be due to several causes. For a correct understanding of the physiologic mechanism involved it is necessary to differentiate between these possible causes.

The most common cause of the symptoms of shock is free hemorrhage. It should be emphasized that all persons do not react the same to loss of blood and that the estimation of hemorrhage during operation is very inaccurate.

Another common cause of shock is trauma to the viscera. Under this condition shock is due to loss of circulatory fluid in the traumatized areas, mainly brought about by a local peripheral mechanism.

Shock produced by excessive nerve irritation under an anesthetic is probably a much more rare occurrence than clinical reports would

seem to show. The mechanism involved in these cases is unknown. In cases of fractures and operations involving trauma to large areas of fat in which shock is diagnosed, pulmonary fat embolism may be a cause.

Some of the endocrine glands, particularly the suprarenals, are factors in some causes of shock; but it is very difficult to determine to what degree they participate as primary active agents in producing the state, or how much they are affected by the low blood-pressure and the changes incident to the condition itself.

The nerve impulse probably bears no quantitative relation to shock.

Deep etherization may produce most of the symptoms of shock. The continued depressed state following deep anesthesia, while primarily due to the anesthetic, is soon complicated by the resulting factors of low blood-pressure, subnormal temperature, and other changes.

Some cases of the conditions diagnosed as surgical shock may be due to a combination of deep anesthesia with reflex inhibition of respiration.

Ether certainly does block afferent impulses to the higher centers, but some of the reflexes involving the medullary centers, particularly those which inhibit respiration, are not blocked when very strong stimuli are employed.

REFERENCES

1. Mann, F. C.: The peripheral origin of surgical shock, Johns Hopkins Hosp. Bull., 1914, xxv, 205–212.
2. Meltzer, S. J.: The nature of shock, Arch. Int. Med., July, 1908, pp. 571–588. Seelig, M. G.: The nature of shock, Internat. Abst. Surg., 1914, xviii, 117–123. Vale, F. P.: Concerning shock, Med. Rec., lxvi, 325–330.
3. Mann, F C.: Shock and hemorrhage: An experimental study, Surg., Gynec. and Obst., 1915, xxi, 430–441.
4. Henderson, Yandell: Acapnia and shock, I, Carbon dioxid as a factor in the regulation of the heart-rate, Am. Jour. Physiol., 1908, xxi, 126–156; Acapnia and shock, II, A principle underlying the normal variations in the volume of the blood stream and the deviation from this principle in shock, ibid., 1909, xxiii, 345–373; Acapnia and shock, III, Shock after laparotomy: Its prevention, production, and relief, ibid., 1909, xxiv, 66–85; Acapnia and shock, V, Failure of respiration after intense pain, ibid., 1910, xxv, 385–402; Acapnia and shock, VI, Acapnia as a factor in the dangers of anesthesia, ibid., 1910, xxvi, 260–286.
5. Janeway, H. H., and Ewing, E. M.: The nature of shock, Ann. Surg., 1914, lix, 158–175.
6. Morison, R. A., and Hooker, D. R.: The vascular tone and the distribution of the blood in surgical shock, Am. Jour. Physiol., 1915, xxxvii, 86–93. Muns, W. E.: Changes in the peripheral circulation following intestinal trauma, Proc. Soc. Exper. Biol. and Med., 1914–1915, xii, 87–90. Seelig, M. G., and Lyon, E. P.: The condition of the peripheral blood vessels in shock, Jour. Am. Med. Assn., 1909, lii, 45–48.
7. Hill: Further advances in physiology, London, 1909, p. 178.
8. Ranson, S. W., and Billingsley, P. R.: The conduction of painful afferent impulses in the spinal nerves, Am. Jour. Physiol., 1916, xl, 571–584. Ranson, S. W., and von Hess, C. L.: The conduction within the spinal cord of the afferent impulses producing pain and the vasomotor reflexes, Am. Jour. Physiol., 1915, xxxviii, 128–152.

9. Porter, W. T.: The effect of uniform afferent impulses on the blood pressure at different levels, Am. Jour. Physiol., 1907–1908, xx, 399–406. Porter, W. T., Marks, H. K., and Swift, J. B.: The relation of afferent impulses to fatigue of the vasomotor center, ibid., 444–450.

10. Mann, F. C.: References 1 and 3.

11. Forbes, A., and Miller, R. H.: Detection with the string galvanometer of afferent impulses in the brain stem and their abolition with ether anesthesia, Am. Jour. Physiol., 1916, xl, 148–149.

12. Forbes, A., McIntosh, R., and Sefton, W.: The effect of ether anesthesia on the electrical activity of nerve, Am. Jour. Physiol., 1916, xl, 503–513.

13. Bissell, W. W.: Pulmonary fat embolism—a frequent cause of postoperative surgical shock, Surg., Gynec. and Obst., 1917, xxv, 8–22.

14. Porter, W. T.: Shock at the front, Boston Med. and Surg. Jour., 1916, clxxv, 854.

15. Elliott, T. R.: The action of adrenalin, Jour. Physiol., 1905, xxxii, 401–467.

16. Cannon, W. B., and De La Paz, D.: Emotional stimulation of adrenal secretion, Am. Jour. Physiol., 1911, xxviii, 64–70.

17. Corbett, J. F.: The suprarenal gland in shock, Jour. Am. Med. Assn., 1915, lxv, 380–383.

18. Bedford, E. A., and Jackson, H. C.: The epinephric content of the blood in conditions of low blood pressure and "shock," Proc. Soc. Exper. Biol. and Med., 1916, xiii, 85–87.

19. Bedford, E. A.: The epinephric content of the blood in conditions of low blood pressure and shock, Am. Jour. Physiol., 1917, xliii, 235–257.

20. Stewart, G. N., and Rogoff, J. M.: Liberation of epinephrin, Jour. Pharmacol. and Exper. Therap., 1916, viii, 205; Liberation of epinephrin from adrenals, ibid., 479; Epinephrin content of adrenals, Jour. Exper. Med., 1916, xxiv, 709.

21. Unpublished data.

22. Gatch, W. D., Gann, D., and Mann, F. C.: The danger and prevention of severe cardiac strain during anesthesia, Jour. Am. Med. Assn., 1913, lx, 1273–1278.

23. Boothby, W. M.: The determination of the anesthetic tension of ether vapor in man, with some theoretical deductions therefrom, as to the mode of action of the common volatile anesthetics, Jour. Pharmacol. and Exper. Therap., 1913–1914, v, 379–392.

24. Gatch, W. D.: The effect of laparotomy on the circulation. Tr. Am. Gynec. Soc., 1914, xxxix, 180–192.

25. Bernstein, J.: Ueber die physiologische Wirkung des Chloroform's in Moleschott, J.: Untersuch. z. Naturl. d. Mensch. u. d. Thiere, Giessen, 1870, x.

WAR'S INFLUENCE ON MEDICINE
Presidential Address *

C. H. MAYO

AMERICANISM

The medical profession should feel proud of the position it has attained in the affairs of the world. It has been second to none in its progress, and medicine has now become nearly an exact science. The exalted position of medical men throughout the world's war has become accepted and has given them an opportunity to apply wholesale, as it were, the newer methods of prevention and treatment of disease by adopting at once fixed medical standards. The enormous value of this practical application relieves the necessity of a slower advance by discussions with the ignorant and by overcoming obstructionists. Hundreds of our medical men, appreciating the needs of the people as well as the requirements of soldiers, have long since accepted medical service to aid humanity in all the countries of Europe. There will be no need of conscription for medical men. They will be ready long before the army is ready.

The medical profession was first to mobilize, and has been signally honored by the Government in having given to it the first flag to be carried abroad, thus signifying our country's active entrance into the war. No worthier representative of the profession could have been chosen as standard bearer than Dr. George W. Crile, who had done so much to develop the base hospital idea. These accomplishments give us a right to discuss Americanism. As a people we cannot accept the Prussian point of view that war is of divine origin, and that those killed in waging it pass immediately to Walhalla. We are more than ever firmly convinced that war is what Sherman called it, and made of it— Hell. In beginning and conducting war, autocracies, government

officers, and soldiers each are responsible to the laws of humanity. In all the world's history war has occurred at fairly regular intervals, and the great steps of man's progress have been closely associated with it through advances made by autocratic order and accepted through discipline. The very fact that a people can respond to so great a catastrophe as war shows that they are capable of the progress which, regardless of the human sacrifice, is the ultimate goal. Democracy is not achieved in a day. Russia has only started on her freedom along these same lines, to be ultimately united only through either the present war or an internal revolution. Autocracy and imperialism are hanging in the balance, and the scale will turn with education and opportunity for the people. Our own nation has never been in any war of conquest, having fought only for the "rights of life, liberty, and the pursuit of happiness for all," and having paid for all territory taken. War gave us freedom, our institutions, and the consolidation of our states; it gave to the world the freedom of the seas, and it gave to Cuba the same liberty that is in time to come to the Philippines and other of our possessions. Our war of freedom was instrumental in effecting such changes in the governing methods of our mother country—England— that she has since so endeared herself to her other colonies that they have freely bled themselves white in their loyal support of her. Our original displacement of the Indians must be regarded as being somewhat similar, though much more humane, than Germany's attempt ruthlessly to stamp out what it considers weaker, non-aggressive, or decadent people who, from its point of view, are wasting the world's supplies. Germany plans that her defeated opponents are to be restored to usefulness by "Kultur," a proposition the value of which is open to discussion. Laws are either natural or man-made. Obedience to law means life and liberty.

In our own county our constitutional form of government is founded on personal liberty. It is stronger for its just recognition of property rights, and ultimately the will of the people prevails. Since the framing of the constitution, thirty-two millions of emigrants have come to our country. Those who came early aided in developing it from the wilderness, and at once became loyal citizens. Those who came late, to obtain opportunity and material benefit and to avoid the restrictions, oppressions, and conscriptions of their own countries, are not truly our citizens, becoming so only in the second generation. The state, acting as our monarch, controls the rates and the taxes. It provides for the care of

the helpless, deficient, and insane.   It protects the health and lives of its people, is constantly working to benefit all by such acts as the compensation law, and is now discussing a modification of the compulsory health insurance of Germany and England.

The great industries have in the past unnecessarily destroyed thousands of human lives and turned on the public many more thousands of cripples dependent on public charity.   It has been cheaper for these industries to let Europe pay the cost of bringing individuals to maturity and to replace the injured and lost with new human material than to go to the trouble and expense of providing suitable means for protecting the lives and limbs of employees.   Today we are face to face with the truth that we must arise and upbuild our own people.   The economic law of supply and demand has gradually been brought into force, and the waste of human life must cease.   We hear on every hand of projects and efforts for the conservation of human life, a movement which is not the outcome of any philanthropy or sentiment but of necessity.   Men can no longer be replaced with the old-time ease, and their individual value to the community has increased accordingly.

Economic necessity, not sentiment, has given almost sovereign power to health departments, both state and municipal.   The physical condition of school children is being looked after under the supervision of physicians and trained nurses, and even food is being furnished that the young may develop well and grow strong to do the world's work.   To prevent sickness among those who are well and bring the young to maturity with health and education is the most important business of the state.

The evolution of many large institutions has come about through the development of the by-product.   The by-products of human deficiencies, mental, moral, and physical, are a clog and a burden to the state.   In our great hospitals for the insane we find that much effort is being made by highly organized and expensive methods to reclaim the mentally affected.   These institutions have become not the madhouses of the past, but hospitals for the mentally sick.   The expense is great, the percentage of cures small, but well worth the effort.   University and state hospitals are needed for the care of the poor, for curing blindness, and for restoring cripples and defectives from birth and injury to health and usefulness.   Now that the war is producing injuries by the thousands, a new impetus is given this work, that by training in special employment and artificial aids such persons may be as happy as possible,

and self-supporting. It is through organized effort in the medical profession that so many of these great things of the world's work have been accomplished. Within half a century, many years have actually been added to the average life of man. This has been largely accomplished by preventive medicine as well as by advances in the cure of disease.

The American Medical Association has an advisory committee, under Dr. Alexander Lambert, investigating the question of compulsory health insurance for the information of the profession. Such laws being meant for the general good of the people, physicians should not obstruct, but should discuss and help in devising methods whereby the needy will receive aid, the middle classes will not be pauperized, and this without detriment to the medical profession. Anything which reduces the income of the physician will limit his training, equipment, and efficiency, and in the end will react on the people.

One of the greatest functions of a state is the development and control of its educational system. Compulsory school attendance and child labor laws have been necessities. It will soon be generally recognized that the citizen is best made when a child. Compulsory school attendance through the seventh grade and all general knowledge obtained through the English language are necessary to this citizenship. Other languages than English are special studies. Private schools should be encouraged, but all should be subject to state inspection and control. Private schools conducted by hyphenated Americans should be subject to government inspection to remove them from the protective influence of local and state politics. The lack of unity of our nation is largely due to lax educational laws which allow emigrants to develop community and educational interests in the language of their fatherland and not to live up to our constitution. As a people our prestige in the world has been injured most unfortunately by the petty jealousies and the local interests which have been made general through intrigue and political effort. Especially have we decried to the world the acts of Government officials whom we ourselves have placed in power. More good would come to our country through tongue control than birth control. Our best people must come to the fore, and if necessary, by self-sacrifice, do their part in the political management of the local, state, and general affairs of our country if democracy is to survive. A wise monarch in Europe has remarked that it is surprising how often Americans seem pleased at being mistaken as coming from some other country. Our emigrants from all countries desire opportunity for expansion, thought,

and individualism.   With opportunities, their brain-cells create great
inventions and ideas.   It is most natural that such people should de-
velop in this country of opportunity, and in theory it is just as natural
that much of the new thought in the world's progress may come from the
Siberian people after the next two generations in America.

In a review of the world's progress in the last hundred years the
wonderful part our country has played in it is at once manifest.   Man's
power to control the elements was developed in America.   Franklin
was the first to draw electricity from the clouds.   Morse developed the
telegraph, Field laid the first cable, and Tesla, through his American
education and opportunity, developed electric control.   We still thrill
at the story of Fulton's first steamboat, the *Claremont*, on the Hudson
River.   The Howe sewing machine took sorrow from "the song of the
shirt."   Alexander Bell developed the telephone, and Edison the phono-
graph; Holland developed the submarine, while Langley, followed by
the Wrights, gave us the airship.   The typewriter, the adding machine,
and nearly all mechanisms, systems, and inventions for conserving time
and increasing productiveness have been American in origin.   Within
scarcely fifty years modern farm machinery—planters, seeders, mowers,
reapers, binders, and threshers—has here increased man's ability a dozen-
fold, while in Europe the sickle, the cradle, and the flail are still being
used.

I mention these things here because the great medical profession of
this country has not stood as a united body of that which is American in
medicine.   Many, while abroad, have apologized for medical conditions
at home, and for personal advancement have often written of and dis-
cussed as remarkable European discoveries that are trivial in comparison
to our own.   Many important discoveries in medicine in America have
not been accepted here until they have been appropriated by Teutons and
returned to us with the stamp, "Made in Germany."   Our country has
done much for the advancement of the medical profession through the
enactment of just laws requiring standards of education.   Through the ef-
forts of the Council on Medical Education, of which Dr. Arthur D. Bevan
is chairman, our profession has largely aided in the standardization of
medical colleges.   Through the work of this board, many of the in-
efficient medical colleges have been forced to close, to the great ultimate
good of medical science and of the people served by their graduates.
The added requirements of preliminary education and increased years
of medical study were so great, however, that with the elimination of 40

per cent of the colleges, and the years of study more than doubled, we have little more than one-third as many students of medicine now as in 1900. Fewer doctors, better trained nurses to take some of their work, better educated people, and preventive medicine to reduce sickness maintain an even balance, however. Now will come a hysterical demand to lower the bars of educational medical requirements under pretext of the necessity of war. It must not be permitted. If ever we need educated men, it is now, and they will continue to be needed.

To our credit it may be said that today our graduates in medicine by education and training are equal to those of any country, and better than those of most countries of the world. The cost of conducting medical schools is so great, as compared with the fees received, that they may be conducted only by richly endowed colleges or state universities. It costs the state of Minnesota $4200 to educate a physician, but its people are well paid for the expense incurred, as they receive the best medical care. Minnesota now stands fourth among the states in health service for the people, and was the first to inaugurate state board examinations to regulate the practice of medicine. However, the standard for the practice of medicine is now high in most states, and here I would pay tribute to the excellent work of the National Board of Medical Examiners developed through the efforts of the late Dr. William Rodman while President of this Association. In some states, through local or state influence, many forms of the practice of medicine have been given separate boards of examiners, based wholly on lines of treatment. There should be no examination as to the method of treatment. Ultimately, when, as the result of existing laws, general standards of education are higher, public demand will require that all who practice the healing art shall be tested on educational lines, both general and special, the latter wholly on the knowledge of the facts of anatomy, histology, chemistry, sanitation, preventive medicine, and the diagnosis of disease, but not on treatment, before permission is given to care for the lives and health of the people.

During past centuries medicine has advanced slowly, but quite as rapidly as other lines of endeavor. The wonderful advance of the world's affairs during the last century, and especially in the latter half of it, has given us a new world in thought and productive activity. In medicine this has been especially true in the development of our knowledge of the bacterial cause of disease and its prevention and treatment. How proud the French are of the wonderful part Pasteur played in the discoveries

and investigations that disclosed a new microscopic world of life! We now know that to bacteria is due the essential chemistry of existence, as they maintain life by changing inorganic material into solutions for plant food. All multicellular organisms, both plant and animal, are subject to disease and destruction through the action of the single cell organism. Our progress in the world's work will be to further recognize and classify bacteria, to propagate and train them to become man's true slaves, and to control, render harmless, or destroy those destructive to life. The French, through Madame Curie, gave to us the knowledge of radium. England is proud of Lister, who elaborated the work of Pasteur into a benefit to surgery, showed that infections are caused by bacteria, and thus developed antiseptic surgery. There also was developed the Crookes tube, the penetrating rays of which were accidentally discovered by Roentgen, from the fact that photographic plates in the room were affected by them.

We have all benefited by Germany's elaboration of scientific problems; especially by her proof to the world of the benefit of teamwork and organized national discipline over the efforts of the individual. It can be said of many scientific discoveries that they were thought of years ago by men who lived before their time, as it were; yet credit must go to those who overcome resistance, educate the people, and compel acceptance. From a medical standpoint we must be proud of our country and our great dead. The work of McDowell, of Kentucky, who performed the first ovariotomy in 1809, and the impetus to medicine given by Gross, Rush, Sims, Emmett, Senn, Davis, and J. B. Murphy, our former president, and a host of other distinguished dead who added so much to our knowledge of medicine, are known to the world. What a debt we owe to Long for his discovery of ether, which made modern surgery possible and childbirth easier!

We are proud of our agricultural department and its investigations as to the causes, control, and cure by serums of the diseases of animals and the destruction of parasitic hosts. The work of Erwin F. Smith on plant diseases is monumental, especially his discoveries as to the cause of certain plant tumors which show again that our bacteria and insect chemists are the prime offenders through the development of their varying acids, which may be stimulating or destructive to other cell life, causing tumors or decay. We should appreciate and aid the work of these departments.

EDUCATION

Whereas a hundred years ago the educated man could acquire the bulk of all that was known, it is now commonly recognized that the world's knowledge is so extensive that the more general an education a man receives the more hampered he may be, unless he is also highly educated along some particular line. There are specialists in every line of human endeavor—the educator, the professional man, the business man, the farmer, and the laborer. Flexner is right in his effort to bring about a change in the prevailing system of education, founded as it was in the monk's period of the world's progress. It is essential to adjust education to man's requirements and necessities of today, but much general discussion will be necessary to change public opinion. Already some of the preparatory schools have started a propaganda against even the trying out of experimental changes in educational forms. The graduating age of twenty-nine in medicine is four years too late, as the most productive and ideal period of thought is thereby limited to too short a time. The graduate's best work must be accomplished in the next fifteen years, when his brain-cells are most energetic and receptive. It is well to remember that death overtakes the average physician at the age of fifty-eight. The intellectual man and woman marry late or not at all, and the resulting birth-rate does not exceed one-third of their original number. In order that the physician may be graduated at the age of twenty-five, his vocation should be chosen in the seventh year of school life in order that special lines of study may be begun, and the eighth grade, the work of which is a review, should be eliminated. A revision of the time devoted to a study of the classics is necessary. Four years of Latin for the study of the scientific professions is a just proportion. The work of the last year of high school and preparatory school should not be reviewed in the first year of college, thus saving two years. By proper specializing in a six or seven year combined course of college and medicine, the student should be entitled to two degrees, such as are now given in the University of Minnesota.

Medicine has been divided into many branches and, of necessity, diagnostic team work has developed, with the result that both the rich, who can pay, and the very poor, who cannot pay, secure the best possible service. To secure equally good service for the great bulk of the people, however, some change in diagnostic methods by the establishment of

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centralized plants, hospitals for diagnosis, or combinations of those engaged in specialties to care for the extraordinary cases is necessary.

WORK OF ARMY MEDICAL OFFICERS

War has always had a great influence on medicine, first developing the priest physician, then the barber surgeon, and later the army medical officer. In war time Paré devised the ligature for arteries, although he was not the first to employ it. Napoleon, who was often at a loss to supply his army with food, made awards, which from an empiric and practical standpoint developed canning and the preservation of food before bacteria were known. The American medical profession will ever be under obligation to our army medical officers for their services to the world in the discoveries of numerous diseases, their causes and prevention. Our army medical officers stand preëminent in science. To Beaumont we are indebted for the first report on digestion, digestive fluids, and gastric movement from direct observation of a patient with gastric fistula. To Surgeon-General William Hammond we are indebted for the development of the army medical museum, the second in the world. Surgeon J. S. Billings fostered the second largest and the best medical library in the world. Surgeon-General Sternberg discovered the pneumococcus and founded the army medical school and the Government laboratories of bacteriology and hygiene. Under Sternberg's administration Major Walter Reed, with James Carroll, Jesse W. Lazear, and Aristide Agramonte, proved the mosquito to be the agent transmitting yellow fever. Lazear lost his life from the disease during the investigation. To these men belongs the credit for the control of yellow fever throughout the world, although the theory had been advocated by J. D. Nott in 1848 and Carlos Finlay in 1881. Through the knowledge obtained by this board and the sanitary and hygienic investigations of the Army Medical Service, General Gorgas, a former president of this association and now surgeon-general of the army, was able to free Havana of contagious disease. Yellow fever disappeared from Havana for the first time in one hundred and fifty years. Under the supervision of General Gorgas the Panama Canal zone also was freed from both yellow fever and malaria. The latter was proved to be a mosquito-borne disease by Major Ross, of the British army. This sanitary work made possible the building of the canal, and the health conditions in Panama are now better than in our own country. To Robert Maitland O'Reilly, one time surgeon-general of the army, we are indebted for the

reserve medical corps developed for the expansion of the medical service during the time of war, and under which service several thousands of us are now preparing to do our bit. Under Surgeon-General George H. Torney was instituted the first compulsory vaccination for the prevention of typhoid. This was made possible by the discoveries of Chantemesse and Widal in France and Sir Almroth Wright, of England, though to Major Frederick F. Russell, of America, is largely due the credit of its development. On the Mexican border Major Russell has vaccinated more than 20,000 United States soldiers at one time and put a stop to typhoid. To understand fully what this means, we must realize that the medical army service is as much a specialty in the care of soldiers as any specialty can become. In almost impossible conditions and surroundings to prevent and care for disease and infections, employ all of the serum and vaccines known, and be fully conversant with all sanitary and hygienic laws requires, indeed, special training. During the Spanish War, 20,000 cases of typhoid occurred among our troops in training camps between May and September, 1898. Of the volunteer soldiers, 90 per cent developed typhoid within eight weeks of camp life. Investigations by Majors Walter Reed, Victor Vaughan, a former president of this association, and Edward Shakespeare did much to demonstrate the methods by which diseases are transmitted by flies and human carriers, and also by utensils and camp pollution. In our volunteer army in Cuba 450 soldiers were killed, and 9853 died of disease. The benefit to our country after the present war in having some thousands of medical officers trained in sanitation, hygiene, and the prevention of disease will be incalculable. Through lax examinations of recruits and the natural effects of prolonged life and overcrowding in trenches and underground structures, tuberculosis will become a menace to our soldiers, as it is today in France.

In the American occupation of Porto Rico in 1898, smallpox, which was always present, became epidemic, 3000 cases occurring in two months. By order of Governor-General Davis and under the direction of Major John Van R. Hoff, the island was absolutely rid of the disease by the vaccination of all the inhabitants—more than 800,000 people. There also Captain Ashford and his board have treated over 300,000 people for hookworm disease, reducing its mortality 90 per cent. A similar work with like results has been carried on in the Southern States through the generosity of Mr. Rockefeller through the work of his foundation, largely aided by the army medical and public health services.

Mention should be made also of the work done by army medical men in the study of pellagra. Beriberi has been eliminated from the Philippines by the investigations of the preparation of rice made by Captain Edward Vedder. Surgeon-General Torney advocated the Army Dental Corps and the Army Corps of Nurses. The present war is one of remarkable proportions, and the medical service has assumed an importance such as it never had before. The old army hospital gangrene is a thing of the past. A knowledge of the care of infections, prevention of tetanus, vaccination for smallpox and typhoid, the cause and prevention of typhus, the old camp fever, also cholera, the plague, and fevers of all sorts, including the new trench form, is a training requirement of the army medical officer, and results in the restoration to duty of a high percentage of the injured.

The requirements of our profession have been raised from within, and not forced from without. The American College of Surgeons deserves great credit for establishing its high standards for the science of surgery and the honesty of the surgeon. Through immediate necessity, hospitals are rapidly being classified and standardized that they may become more efficient for the people and for the training of nurses and future physicians. As a body, no profession has more power if wisely used. The period of discussion with fanatics and cults as to the cause and prevention of disease, a long period in medical history, is past, for today disease can be checked by order. Our country should secure a medical cabinet officer in the near future.

We must aid in all that will elevate the general standard of, and conserve, the American citizen. Prohibition is a war measure the value of which is beyond discussion. That disease was frequently water-borne is a practical observation that has existed for many centuries. To a large extent among the Orientals the danger of such transmission was overcome by the drinking of tea and coffee, the water for which was purified by boiling. In Europe the same results were obtained in the manufacture of weak wines, brews, and liquors, the fermentation and yeast germs of which destroyed the virulent bacteria. Now that we know how and why water was dangerous, the necessity especially of alcoholic drinks has been removed in every community in this great country by an abundance of pure water. No one except the policeman sees more of the results of overindulgence in alcohol, demonstrated by poverty, sickness, immorality, and crime, than the physician. Medicine has reached a period when alcohol is rarely employed as a drug, being

displaced by better remedies. Alcohol's only place now is in the arts and sciences. National prohibition would be welcomed by the medical profession.

American dentistry has made a place for itself in the world, and America stands at the head of all countries in the care of the teeth. We are all proud of the work of American dentists. We may pay our tribute also to the American nurse, who has distinctly elevated the nursing of the world and care of the sick. Her experience and training make her the best wife and mother and a leader in support of the best in education and discipline in her community.

It is most fortunate that our army, navy, and public health medical services are in the hands of three of our ablest men, Surgeons-General Gorgas, Braisted, and Blue, and we must laud the work of the general medical council under the able directorship of Dr. Franklin Martin. The Journal of the American Medical Association, under the direction of Dr. George H. Simmons, has been an important factor in the education of the American physician.

Medical men, your country needs you now and always! You must remember that the state is permanent and does not exist for the good of the individual, but that the individual exists for the good of the state.

MEDICAL SERVICE IN THE UNITED STATES ARMY*

C. H. MAYO

It is a frequent hackneyed argument that in view of our assumed higher intelligence war is incongruous and inexcusable. Nevertheless, though there are religious orders opposed to war, the most terrible wars have been waged in the cause of religion. We have both pacifist individuals and pacifist nations, yet as individuals and as nations they do not hesitate to reap the benefits of the strain and stress endured by others without danger to themselves. Armenia and large sections of China, which are pacifists as nations, however, have reaped little but trouble. War will ever continue to occur from time to time, and however started, will advance existing conditions in thought, science, and efficiency.

Our nation is becoming soft, dissipated, and inefficient. From 25 to 50 per cent of our youth from twenty to thirty years of age are physically defective from preventable causes. We make many laws, but obey few; and having an abhorrence of discipline, we discuss freedom. Two years of war with discipline and sacrifice will make of us the greatest nation on earth.

In invention the greatest incentive comes during war, and in four years as much progress will be made throughout the world in this line as would be accomplished during many years of peace.

Concerning medicine, the world will accept without question what has been proved in preventive medicine and in the care of wounds. In view of their limited numbers, the army medical officers have added much to the development of modern medicine.

In education, as a result of the war, schools for the blind and crippled have already been developed far in advance of any previously existing. Education is the essential. We must amalgamate the millions of immigrants from all countries, speaking nearly every language, by refusing to permit them to conduct schools of general education in the language

of their home country.   Children of foreign parentage thus educated in the English language will make American citizens.

In the struggle for existence all cell-life is in a natural state of strife, the ultimate goal being apparently the survival of the fittest.   Nothing endures unless it is of use in the world and in the economy of nature. Man, the highest type of life, cannot evade this natural law.   Variations of animal forms are developed as by-products, as shown by protective color, form, and food in insect and animal life, as well as in plant life.   For reasons of real or fancied wrong or for gain, man who has higher intelligence and who, in the struggle for existence, has acquired memory above instinct, engages in combat to achieve supremacy—a condition called war when tribes or nations are involved.   In the struggle for victory the strongest and best prepared wins; therefore, victory does not always come immediately to the side of the just, although peace is not assured until it does.

Apparently the higher degree of civilization of modern times has developed more diabolical methods of conducting war than those of the past.   The records of the wars of past ages show that while destructiveness and frightfulness played their parts, they were not so effective as in the present period, when higher intelligence prevails.   The records also show that the wars of the past were terminated to a larger extent by medical failure than by any other cause. Sickness was far worse than the bullets of the enemy.   In the wars of a couple of hundred years ago only the officers had surgeons, who were also their barbers.   Medicine was not so advanced during that period that it could be free from charlatanism or supposed secret methods of practice.   Curiously enough, the first people to appreciate the benefits of medicine in its modern application were those who came last into civilization—the Japanese, a small nation which, almost wholly through medical efficiency, was able to fight a much larger nation to a draw.

In recent times, through army officers and war boards, the great nations have prevented their medical officers from doing their full duty because, like that of law, the conduct of war has been established by precedent.   While in the records of the Crimean, Civil, Boer, and Spanish wars, much is said concerning temporary losses from the inefficiency of battleships, artillery, and infantry, the real cause of failure was lack of medical preparedness through the fault of the army officers and not of the medical officers.   The last atrocious medical failure was that of the Mesopotamian invasion by the British.   This was even worse than our

failure to care for our troops while they were in training for the Spanish war, when 20,000 soldiers developed typhoid within five months, the medical officers having no rank or authority to use the ordinary precautions against disease by the employment of simple methods of sanitation and hygiene.

It should be appreciated that today the destructiveness of war by injury is no greater than it was in our Civil War. In fact, the casualty list is not as high as for the men who were engaged in several of the battles of the War of the Rebellion, when the actual loss through lack of medical care was enormously greater. The modern medical officer, by the use of vaccines and serums, prevents the former ravages of eight deaths from disease to one from direct injury.

It is to be hoped that Congress will advance the rank of the medical officers, not only of the regular army, but of the Officers Reserve Corps while they are in service, and not discriminate between the navy and the army. This will stimulate volunteer medical service and our soldiers will receive full protection in their time of need. There is no excuse for our Government to humiliate these men who are highly trained in their profession and who have always faced danger as a part of their duty, and are ready to continue to do so in the service of their country if their authority through rank is made commensurate with their responsibility.

Our democracy has always scorned rank, but Washington finally rose to lieutenant-general, Grant became first a lieutenant-general and in 1865 a general, both through special acts of Congress. The chief medical officer of the army is brigadier-general. Colonel Gorgas was made major-general by a special act of Congress, and it is a mere coincidence that he is surgeon-general at this time. The surgeon-general is not a member of the war council. This is another of the conditions such as brought about the Mesopotamian failure.

The medical officer's rank was low, and in the navy three years ago medical affairs were in a serious state until Congress raised the official position to equal that of medical officers in the navies of foreign countries visited by our navy in time of peace. Previous to that time a great part of the medical service was handled by contract surgeons. There now are six rear-admirals, ranking as high as major-generals, and many colonels. The result has been that the medical officer positions in the navy were early filled by volunteers after the present war was declared.

Nearly all adults have been at some time infected by tuberculosis. The bacilli of such focal lesions are not always destroyed in apparent

recovery, but may be encapsulated, and by the conditions of trench life these local foci are revived.   Thus it is that France has now 150,000 cases of tuberculosis among soldiers and 500,000 cases among civilians. Germany suffers as much, and tuberculosis is one of the conditions which will confront us during and after the war.   Inefficient medical examination compelled the return of a considerable number of the Canadian troops after all the expense of preparation and movement to France. The training in sanitation and hygiene of our army medical officers will enable us to deal with the problem when it comes back to us, but our people also must be educated as to our needs.

The Medical Officers Reserve Corps is being as well drilled as the army officers.   Such training develops men, hardens them, and prepares them to submit to and to insist upon discipline.   It will enable them to exert authority in the lines in which they have been educated, as well as make them feel that they are the equal of the army officers in the management of the privates and can take temporary command if necessary. This training would be superb if, in addition, instruction in sanitation, hygiene, and the treatment of injuries and infections, and special training in the lines of their medical service, could be given.   Such instruction is greatly needed, for, while it is supposed that this primary knowledge is possessed by all physicians, very frequently the lines of their medical application or specialty have in no way fitted them for army service.   The army needs 20,000 physicians.   I believe we shall get them.   Some hundreds of our physicians have already been helping all the nations engaged in this great war, having volunteered their services long since, purely in the interests of humanity.   It would be most unfortunate if, because of a failure on the part of the regular profession to come forward, those practising the various cults and fads of medicine are admitted to the Medical Officers Reserve Corps by Congress on the contention that the half-trained are better than none at all.   The dentists are volunteering, and it is now planned that there will be one dentist for every 1000 recruits, and that soldiers are not to be rejected for ordinary diseases of the mouth and teeth, as they will be looked after while in service.   In this respect we are in advance of all the countries at war except Canada.   Schools of chiropody have been started by the Government in the larger military camps, one special man being trained for each 100 recruits.

That medical difficulties will arise in our own country is evident from the fact that already in some communities the doctors have joined the

Officers Reserve without consulting one another, thus leaving the people of their communities uncared for. The railroads and hospitals must be looked after, and there should be more careful consultation in county and · state societies to arrange medical service so that our home people may not be too seriously neglected. This is a vital point.

We have in this country approximately 140,000 physicians; we lose nearly 3000 of them a year by death. In 1900 it was estimated that about 5500 were graduated each year. The increased preliminary preparation, the added years of study, and the greatly increased expense in the medical profession over that of business, the years of struggle to gain recognition, and the elimination of 40 per cent of our medical schools (the worst ones), have all resulted in a steady reduction of the number of physicians to our population, which has increased nearly 20,000,000 during the same period. Preventive medicine, public instruction as to its benefit, pure water and food, and the work of the trained nurse have made up much of the deficiency.

ABSOLUTELY NECESSARY MICROSCOPIC DIAGNOSIS*

WM. CARPENTER MACCARTY

The rôle which expert microscopic diagnosis plays, and should play, in the practice of the science of medicine may best be appreciated by a study of figures.

The subject may well be treated from three standpoints, each possessing practical and important significance, not only from a diagnostic standpoint, but from a standpoint of justice and efficiency rendered to the general public.

The day of dressed diagnosis and prescription therapy has given way to accurate physical examination and therapy, which knows nothing but the rendition of the most efficient service to the patient, regardless of types of therapy.

The relation of the expert microscopist to this service may be divided into the following three groups of activities from a diagnostic standpoint: (1) Confirmation of clinical diagnosis.   (2) Correction of clinical diagnosis.   (3) Clinical diagnosis.

In so far as pathologic tissues are concerned, each may be seen in the accompanying tables.

There are three points of observation, that is, the clinical, surgical, and pathologic, each of which serves as a means of reckoning the duty which the medical profession owes its clientele.

TABLE 1.—FROM A CLINICAL STANDPOINT

Number of patients registered in July, 1917	4752
Number of operations	1699 (35 per cent)
Number of surgical specimens	1046 (22 per cent)
Number of necessary microscopic diagnoses	208 (4.3 per cent)
Number of specimens removed for diagnosis	179 (3.5 per cent)
Operative cases	(35 per cent)
Operative cases producing surgical specimens	(22 per cent)
Operative cases producing specimens for diagnosis	(3.5 per cent)
Operative cases needing microscopic diagnosis	(4.3 per cent)

It may be seen that, of all patients who come to examination, regardless of the physical ailment, 3.5 per cent cannot be diagnosed clinically, in so far as tissues are concerned, without the aid of the expert tissue microscopist, and that 22 per cent of all patients possess definite pathologic tissues which may, and probably should be, removed.

The question of how many patients possess lesions which must be diagnosed microscopically—bacteriologic, blood, and tissue examinations excepted—may be answered by saying that 4.3 per cent of all patients present tissues which of necessity require microscopic diagnosis. These figures are of the greatest importance in showing the inefficiency of hospital and private practice, which is carried on without the aid of expert tissue microscopy.

TABLE 2.—FROM A SURGICAL STANDPOINT

Number of patients registered July, 1917	4752
Number of operations	1699
Number of surgical specimens	1046
Number of necessary microscopic diagnoses	208
Number of specimens removed for diagnosis	179
Operations yielding specimens	61 per cent
Operations needing microscopic diagnosis	12 per cent

In the second table there is food for thought for the operator who works without the aid of immediate expert tissue microscopy. It may be seen that 61 per cent of all operations yield surgical specimens, and that 12 per cent of all operations require the assistance of tissue microscopy.

TABLE 3.—FROM A PATHOLOGIC STANDPOINT

Number of patients registered in July, 1917	4752
Number of operations	1699
Number of surgical specimens	1046
Number of necessary microscopic diagnoses	208
Number of specimens removed for diagnosis	179
Number of specimens removed for diagnosis needing microscopic diagnosis	149
Surgical specimens needing microscopic diagnosis	19.8 per cent
Diagnostic specimens needing microscopic diagnosis	83 per cent

In the third table the so-called "gross pathologist" may see his limitations in so far as his aid to surgical and clinical procedure is concerned.

Of 1046 surgical specimens, it was absolutely necessary to resort to the microscope in 19.8 per cent, which is practically one out of every five. If such organs as the appendix, gallbladder, and ovary, all of which rarely need a microscopic diagnosis, be excluded in reckoning the percentage, it may be seen that the necessity of microscopic diagnosis jumps up to 28 per cent.

TABLE 4.—PERCENTAGE RECKONED WITHOUT APPENDIXES, GALL-
BLADDERS, AND OVARIES

Number of surgical specimens.................................... 1046
Number of appendixes, gallbladders, and ovaries.................. 321
Number of surgical specimens minus appendixes, gallbladders, and
  ovaries... 725
Number of necessary microscopic diagnoses...................... 207 (28 per cent)

That there is a great organic variability of the necessity for such precision may be seen in Table 5:

TABLE 5.—NECESSARY MICROSCOPIC DIAGNOSES WITH RESPECT TO
ORGANS AND ANATOMIC REGIONS

	Cases	Microscopic
Appendix..	181	0
Breast..	29	5 (17 per cent)
Extremities.......................................	13	7 (5 per cent)
Gallbladder.......................................	84	0
Genito-urinary system.............................	53	7 (13 per cent)
Bladder.......................................	3	0
Epididymis....................................	2	0
Kidney..	20	5 (25 per cent)
Prostate......................................	20	1 (5 per cent)
Rectovaginal septum...........................	1	0
Seminal vesicles..............................	3	1 (33 per cent)
Testicles.....................................	2	0
Vas deferens..................................	2	0
Head...	7	2 (28 per cent)
Cheek (tumor).................................	1	0
Jaw (tissue)..................................	1	1 (100 per cent)
Lip (epithelioma).............................	2	0
Scalp...	3	1 (33 per cent)
Intestines..	28	13 (46 per cent)
Colon...	3	2 (66 per cent)
Duodenum......................................	3	0
Intestine (large).............................	1	0
Rectum..	15	9 (60 per cent)
Rectosigmoid..................................	2	0
Sigmoid.......................................	4	2 (50 per cent)
Lip and glands....................................	3	3 (100 per cent)
Neck...	34	11 (32 per cent)
Glands..	22	7 (31 per cent)
Larynx..	1	0
Parotid (tumor)...............................	6	2 (33 per cent)
Tissue or tumor...............................	5	2 (40 per cent)
Stomach..	14	10 (71 per cent)
Thyroid...	175	3 (1.7 per cent)
Trunk..	11	4 (36 per cent)
Uterus, tubes, and ovaries........................	17	3 (17 per cent)
Uterus...	52	5 (9 per cent)
Tubes..	48	4 (8 per cent)
Ovaries..	56	1 (1.7 per cent)
Sanitarium laboratory.............................	161	64 (39 per cent)
Clinic (specimen for examination).................	46	46 (100 per cent)
Hospital (specimen for examination)...............	34	20 (58 per cent)

The figures shown in the foregoing tables clearly show the necessity of the intimate affiliation of the tissue-pathologist with both the clinician and the surgeon.

It must be remembered that these figures represent activity carried on by men who have been especially trained by a large experience obtained by whole-time devotion to their subject. They are not figures which might obtain in the hands of intern pathologists, or persons who do pathology as a side line, or by professors who teach the subjects of immunology, serology, bacteriology, and postmortem pathology, all under the subject of pathology, but by men who do nothing but study fresh tissues in their relation to clinical medicine.

It may not be out of place at this time to state a few facts relative to other branches of clinical microscopy, each of which is conducted by specialists. During the same month, in which 4752 patients were examined in the Mayo Clinic, there were 4825 examinations of urine, 2000 examinations of blood, 250 examinations of the stool, 165 examinations of sputum, and 258 miscellaneous examinations, all of which were microscopic, and all of which were necessary, either from the positive or negative standpoint.

In summing up these figures it may be stated, from the point of view of the clinical microscopist in all branches, that it was necessary to make 7706 microscopic diagnoses, all of which positively or negatively affected the diagnosis and prognosis of the patients.

There seems to be one conclusion to be drawn from these facts, namely: The practice of medicine to occupy a place in science and to render justice to the patient who places faith in the sincerity and accuracy of the profession, cannot be justly and efficiently carried out without the assistance of expert or specialized microscopy as practised in the various specialties.

THE NEED AND VALUE OF BIOPATHOLOGIC STANDARDIZATION *

WM. CARPENTER MacCARTY

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In reviewing the present status of tissue pathology and its terminology in relation to clinical medicine, it seems that there has been a stationary period of about twenty years in which it has not rendered the greatest degree of efficient service.

It is possible that this period of quiet had its origin in the fact that tissue-pathologists were dealing with end results as seen at necropsy, plus postmortem changes and the imperfections of methods of fixation, all of which probably misrepresent the facts as they exist during life. The resultant conception made upon both pathologists and clinicians is somewhat comparable to that obtained in the study of systematic botany from dried, pressed specimens as compared with that derived from growing specimens in the field, or the conception of birds which is derived from stuffed skins. Such artificial and unnatural methods of study, however, certainly have their place in science and should not be condemned. Without them we should never have reached our present knowledge; but their usefulness as makeshifts is losing its value in the presence of newer methods and observations in pathology, clinical medicine, and general biology.

The second probable reason for the quiet of investigation in tissue pathology may be the fact that bacteriology, with its closely related sciences, such as immunology and serology, has made its greatest advances during the last twenty-five years and has drawn men of vision, imagination, and initiative away from tissue pathology.

The pupils of such great teachers of tissue pathology as Virchow, Cohnheim, Ribbert, Rokitansky, Chiara, Orth, Borst, Welch, Councilman, Hektoen, LeConte, MacCallum, Adami, and others have become immunologists, bacteriologists, serologists, sanitarians, and cancer experts.

The field of tissue pathology has been practically deserted. Hospitals and teaching institutions are beginning to realize the great dearth of efficient men to carry on tissue investigations for clinical diagnostic purposes which they realize are absolutely necessary for efficient medical and surgical practice.

As examples of the necessity of expert microscopic tissue diagnosis to the clinician, surgeon, and pathologist, see Tables 1, 2, 3, and 4 on pages 795, 796, and 797.

These figures clearly indicate that clinical medicine needs tissue experts in order to render efficient service to the patient.

Many clinicians and surgeons have the impression that they can make their own pathologic diagnoses, but this is but an impression which is rarely, if ever, corrected by them statistically. Such impressions must be filled with error in the light of the fact that tissue experts with very extensive experience can diagnose only about 75 per cent of all specimens grossly; and if they rely upon old standards of microscopic diagnosis, they find themselves face to face with a possibility of microscopic diagnosis in only about 95 per cent.

The clinician's clinical diagnostic error is usually thought of as being about 5 per cent. As a matter of fact, in such a superficial organ as the mammary gland his actual error is from 2 per cent to 26 per cent when he makes positive diagnoses. His apparent error, by which is meant that error in pathologic terminology which does not affect the patient, is 8–50 per cent.

His natural acuity and honesty have led him to avoid clinical error in from 1 to 57 per cent of different mammary conditions by utilizing such terms as tumor, nodule, mass, growth, benign (?), malignant (?), or by making no diagnosis.

When he utilized such a term as carcinoma (?), for example, which he does in 8 per cent of his cases (1800), his guess is correct in 57 per cent.[1]

These figures represent the condition of diagnostic efficiency in one organ and compare favorably with the efficiency in the diagnosis of many conditions in other portions of the body, figures concerning which will be published at some future date.

The main factor in which the writer is especially interested at this time, however, is the terminologic inefficiency represented by the clinician's attempt to utilize detailed pathologic terminology for clinical purposes. His code of communication of ideas has an inefficiency of

from 1 to 57 per cent, which is too large to be scientific, although when utilized with the help of tissue pathologists it may not prove inefficient in so far as the patient is concerned, because what the clinician and surgeon really want to know, in the breast, for example, is whether the condition is benign or malignant, operable or inoperable. Clinicians have been led to believe, however, by pathologists that conditions are either benign or malignant, which is only theoretically true.

The theoretic line of demarcation is similar to the one dividing two pieces of property: it has never been seen. The fence, be it one inch or three feet thick, is the practical line of demarcation, and so it is in pathology; there is a practical, histologic, biologic, and clinical line which was first described before this society in 1908.[2] Coincidentally with this description, a new observation was made relative to the role played by regeneration in the life-history of tissues and the recognition of the process of regeneration as a protective process of cells against an antagonistic environment.

It was later recognized that this reaction of cells is similar to the protective activities of all living matter.

It was seen that during the structural and functional evolution of multicellular organisms certain phenomena occurred. Specialization and differentiation of cells were coincident with a diminution of power of reproductivity, which in order to preserve such cells or tissues in the presence of constant or periodic destruction must of necessity be carried on by reserve cells, the function of which is tissue reproduction.

The reaction of these reserve cells (textoblasts) represented cellular hypertrophy, hyperplasia, and migration, which biologically mean hyperactivity, reproduction, and change of environment, and clinically mean benignancy, an indeterminate condition, and malignancy. There is one other phenomenon which is of significance in association with hyperplasia, i. e., attempt at tissue differentiation, which sometimes occurs in the expansive and migratory conditions of hyperplasia. It is well known that the so-called malignant cells (in migratory hyperplasia) attempt differentiation when they arrive in an environment which is favorable to such a change.[3]

It is the lack of this phenomenon in the so-called indeterminate stage which prevents the expert microscopist from prophesying clinically just what will occur. How can he read in undifferentiated cells of living structures just what they intend to do?

It is this stage which has produced confusion among pathologists and

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has caused some to call certain conditions malignant and some to call them benign. It is the stage of cytologic activity which makes the differentiation of some chronic inflammatory conditions from malignant conditions difficult, in fact, impossible.

It is the biologic significance and importance of regeneration with its stages which the pathologists who were dealing with dead tissues and end results failed to recognize.

It is well known that all but a few tissues are capable of regeneration, and in the case of most tissues the reserve cells are recognizable.

The regenerative neoplastic conditions were originally described in the following terminology:[4]

	adeno- cardiomyo- chondro- endothelio- erythro- fibro- glio- leiomyo-	
Primary (restauro-) (benign)...............	leuko- lipo-	
Secondary (expando-) ?...................	lympho- melano-	cytoplasia or neoplasia
Tertiary (migro-) (malignant)..............	myo- myxo- neuro- osteo- perithelio- pilo- poly- rhabdomyo- etc.	

This conception has been and is applied efficiently to tissue diagnosis from a clinical standpoint.

Although it is applicable to regeneration and neoplasia, it is not representative of all the visible biologic phenomena which occur in tissue reaction, and is not, therefore, complete from the standpoint of either the clinician or pathologist, although it has formed a basis for study, correlation, and description of all the other phenomena.

There are six fundamental reactions which manifest themselves microscopically or macroscopically:

1. Cytolysis.
2. Atrophy.
3. Hypertrophy.
4. Neoplasia.
5. Differentiation.
6. Inflammation.

There are seven conditions involved in the basis of the newer conception of pathology and its terminology:

1. Type of cell.
2. Normal activities of cells.
3. Biologic reaction of cells to antagonists in their environment.
4. The degree of reaction of cells.
5. The gross tissue manifestations of cellular reaction.
6. The duration of reaction.
7. The antagonists which caused the reaction.

There are at least 28 different kinds of cells which form human differentiated tissue which constitutes the human organism:

audito-
adeno-
cardiomyo-
chondro-
endothelio-
epithelio-
erythro-
fibro-
glio-
gusto-
leiomyo-
leuko-
lipo-
lympho- } cyte[3]
melano-
myo-
myxo-
neuro-
odoro-
osteo-
perithelio-
pilo-
rhabdomyo-
sebo-
tactilo-
tendo-
visio-

There are three degrees for each reaction:

Cytolysis:
    1. Destruction of the cellular wall.
    2. Destruction of the cellular wall and destruction of the nuclear wall.
    3. Destruction of the whole cell.

Atrophy:
    1. Reduction of the cytoplasm.
    2. Reduction of the cytoplasm and nuclear plasm.
    3. Reduction of the whole cell.

Hypertrophy:
    1. Increase in size of the cytoplasm.
    2. Increase in size of the cytoplasm and nuclear plasm.
    3. Increase in size of the whole cell.

Neoplasia:
      1. Hypertrophy of regenerative cells plus presence of differentiated cells.
      2. Hyperplasia of regenerative cells plus absence of differentiated cells, with or without partial differentiation.
      3. Hyperplasia of regenerative cells plus migration, with or without partial differentiation.

Differentiation:
      1. Partial grouping of cells according to normal grouping.
      2. Incomplete normal morphology of tissue-cells.
      3. Complete normal grouping and normal morphology of tissue-cells.

Inflammation:
      1. The cardinal signs of inflammation (rubor, tumor, calor, and dolor).
      2. Rubor, tumor, calor, and dolor, plus ulceration.
      3. Rubor, tumor, calor, and dolor, plus pus.

The biologic reactions sometimes manifest themselves grossly as:

1. Circumscribed
2. Non-circumscribed
3. Papillary
4. Polypoid   } conditions
5. Cystic
6. Ulcerated

They occur in relation to time as:

1. Acute
2. Chronic } conditions

If these facts be correlated, they arrange themselves in the following manner, which gives a plastic but definite terminologic key to most of the pathologic conditions which we find in tissues.

The clinician can recognize positively only those conditions which are italicized, although he might possibly recognize some of the conditions under the question marks:

```
                                                        ?
                                                  ⎧ audito-      ⎫
                                                  | adeno-       |
                                                  | cardiomyo-   |
                                                  | chondro-     |
                                                  | endothelio-  |
                                                  | epithelio-   |
                                                  | erythro-     |
                                                  | fibro-       |
                                                  | glio-        |
                                                  | gusto-       |
                                                  | leiomyo-     |
           ⎧ circumscribed    ⎫           ?       | leuko-       |   ⎧ cytolysis
 Acute  ⎫  | non-circumscribed |      ⎧ primary ⎫ | lipo-        |   | atrophy
        ⎬ ⟨ papillary         ⟩      ⟨ secondary⟩ | lympho-      ⟩ ⟨ hypertrophy
 Chronic⎭  | polypoid          |      ⎩ tertiary ⎭ | melano-      |   | neoplasia
           | cystic            |                   | myo-         |   | differentiation
           ⎩ ulcerated         ⎭                   | myxo-        |   ⎩ inflammation
                                                  | neuro-       |
                                                  | odoro-       |
                                                  | osteo-       |
                                                  | perithelio-  |
                                                  | pilo-        |
                                                  | poly-        |
                                                  | rhabdo-      |
                                                  | sebo-        |
                                                  | tactilo-     |
                                                  | tendo-       |
                                                  ⎩ visio-       ⎭
```

Time does not permit a detailed elucidation with examples of the application of this conception. Although not yet perfect and complete, it offers a simple conception with a simple code of communication; it is histologically, clinically, biologically, and scientifically more efficient than the chaotic, extravagant, inconsistent, empirical, and clinically inefficient conception and terminology of tissue pathology which has come down to us from that great and essential period of observation and description which shall ever be remembered in association with the great masters of pathology who had a scientific strength of conviction which was great enough to break away from the mystic empiricism of the ages which had preceded them.

In conclusion it must be stated, in the presence of this body of progressive surgeons of America, that this new conception, as it exists, was not possible without a study of early conditions and processes which was made possible by what might be called prophylactic operative surgery as it is being practised in association with expert microscopy.

REFERENCES

1. MacCarty, W. C., and Broders, A. C.: Studies in Clinicopathologic Standardization and Efficiency. Surg., Gynec. and Obst., 1917, xxv, 666–667.
2. MacCarty, W. C.: Carcinoma of the Breast. Trans. South. Surg. and Gynec. Assoc., 1910, xxiii, Mayo Clinic, Collected Papers, 1911, 228.
3. MacCarty, W. C.: The Histogenesis of Cancer of the Breast. Surg., Gynec. and Obst., 1913, xvi, 441–459.
4. MacCarty, W. C.: The Evolution of Cancer. Mayo Clinic, Collected Papers, 1915, 903–917.
5. MacCarty, W. C.: Cancer's Place in General Biology. Am. Naturalist, 1918.

CANCER'S PLACE IN GENERAL BIOLOGY*

WM. CARPENTER MacCARTY

The condition which has been called cancer by the laity and the medical profession has been studied by the latter largely from the standpoint of disease. Investigators have considered its great destructive action, cause, prevention, and treatment, all of which study has been stimulated by the urgent necessity of the eradication of cancer from the ills of man, and not in its relation to the known biologic facts concerning the universal conflict between living normal cells and their natural enemies. In order to approach correctly this biologic phase of the condition, it will be necessary to answer the question: What is cancer?

To the pathologist, cancer is a cellular overgrowth which occurs in some multicellular organism, especially in man, characterized by its apparently unlimited proliferation, during which it destroys tissues and is fatal, eventually, to the whole organism. This, in general, is the conception held by the members of the medical profession, but to the scientific mind interested in and trained in the fundamental or more specific factors operating in living nature, it is neither satisfactory nor sufficient.

An analysis of the condition from such a biologic point of view necessitates also for its elucidation a study of the facts relative to the evolution of multicellular organisms from single cells as units of life. Biologists agree that the cell is the visible unit of life, and that all cells have certain fundamental structural and functional characteristics common to all. They further agree that all multicellular beings evolve by a process of division or segmentation of a single cell which has been stimulated automatically or by the process of extrinsic fertilization to such activity.

During the process of segmentation certain dominant facts present themselves. A fertilized ovum, for example, divides; the cellular divisions divide; these continue to divide and form eventually, in a definite period, the millions of cells which constitute the organism. This is a simple statement of general facts, but coincidentally with these facts

there is an orderly sequence of cellular changes which seems to be fore-ordained in the original fertilized ovum; the cellular progeny does not retain, to the same degree, all the structural and functional character-istics of the original cell (ovocyte). There is a grouping of cells coinci-dent with morphologic and functional differences. Out of such differen-tiation and specialization of cells types of cells arise, groups of which constitute what are called tissues (adenotex, chondrotex, endotheliotex, epitheliotex, erythrotex, fibrotex, etc.) (Fig. 325). Two or more of the different tissues become grouped to form organs (tongue, esophagus, stomach, liver, kidneys, skin, etc.) which likewise are grouped to build up structural and functional systems (respiratory, alimentary, nervous, osseous, etc.), the combined qualities of which form the complete multi-cellular organism or being. Such orderly evolutional facts apply to the development of all animal and vegetable multicellular beings (Fig. 326).

Out of the essential living properties of a single cell other cells de-velop which have in them an exaggeration of some essential initial quality, each tissue representing an exaggeration of some one quality. Such evolutionary cytologic organization produces a communism of living units, the combined apparent and dominant purpose of which is to live and reproduce its kind.

A biologist, if asked the ultimate purpose of life, would shake his head and say he did not know, but asked the immediate and dominant purpose, would say the protection of life, and this protection, even at the expense of life, an apparent contradiction which has been recognized but not comprehended even by scientists. The evidence of this great pro-tective purpose of living matter is too universal to be called to the atten-tion of the least observing; it works automatically and in a large degree independently of the will of living beings.

This fundamental vital protective purpose forms the basis of the fol-lowing consideration of cancer's place in general biology. It presup-poses the fact, and observation substantiates it, that all living cells have natural antagonists against which protection is necessary, and that there is a conflict in nature during which there is constant building up and tearing down of things living. The human body is no exception to this rule, as every physician and layman knows. The tearing down is called disease, and the rebuilding is called regeneration, repair, and healing.

The partial destruction of a human tissue by animate or inanimate antagonists may be followed by its regeneration; the complete destruc-tion may be followed by repair or replacement, but not by its regenera-

Fig. 325.—Some of the differentiated cells (textocytes) of the human body:

Biologic terminology	Medical terminology
1. Erythrocytes	Red blood-corpuscles.
2. Lymphocyte (small)	Lymphocyte (small).
3. Lymphocyte (large)	Lymphocyte (large).
4. Transitional forms	Transitional forms.
5. Leukocytes	Polymorphonuclear leukocytes.
6. Eosinocytes	Eosinophiles.
7. Mastocytes	Mast cells.
8. Fibrocytes	Fibrous connective-tissue cells.
9. Rhabdomyocytes	Striated muscle cells.
10. Melanocytes	Pigmented cells.
11. Myxocytes	Myomatous cells.
12. Cardiomyocytes	Heart muscle cells.
13. Lipocytes	Fat cells.
14. Leiomyocytes	Smooth muscle cells.
15, 18, 19. Adenocytes	Glandular epithelium
16, 24. Neurocytes	Nerve cells (neurons)
17. Osteocytes	Bone cells.
20. Endotheliocytes	Endothelial cells.
21. Chondrocytes	Cartilage cells.
22. Epitheliocytes	Epithelial cells.
23. Tenocytes	Tendon cells.
25. Sudorocytes	Sweat cells.
26. Sebocytes	Sebaceous cells.
27. Gustocytes	Taste cells (of a taste bud).
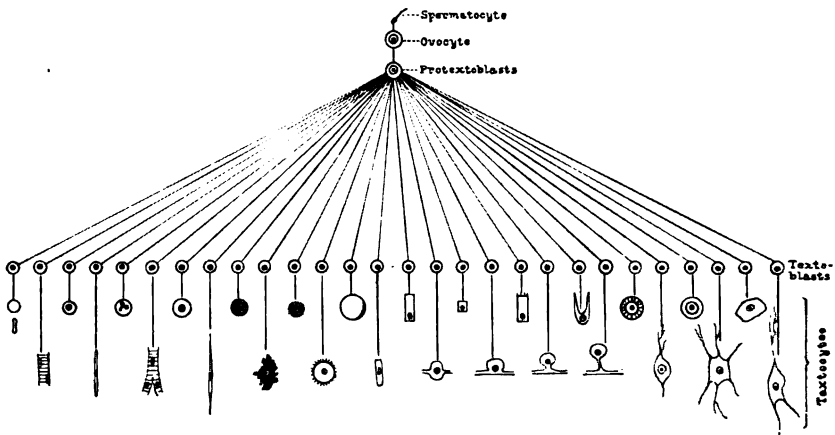
Fig. 326.—In the embryonic evolution of adult tissues there are certain arbitrary stages of differentiation in which the cells may be given certain names.

During segmentation of the fertilized ovum (ovocyte)the daughter cells do not show any special morphologic characteristics of adult tissues, but are nevertheless forebearers of such tissues and may be called *protextoblasts*.

The textocytes, or tissue cells, are represented in this diagram by symbols derived from the characteristic outlines of the cells of specific tissues (Fig. 325).

After the protextoblasts align themselves into the positions of subsequent tissues they become the immediate forebearers of the tissues and may be called textoblasts. These cells develop by differentiation and specialization into the tissues (textocytes) of embryonic and adult life. Some of the cells remain undifferentiated (textoblasts) in adult life to form the reserve or regenerative cells for specific tissues when the latter are destroyed.

tion.*   The degree of regeneration of tissues, according to the observations of biologists, is in an inverse ratio to the degree of their specializa-

* This statement may not seem to be true when applied to some of the lower forms of life, such as the earth worm (*Allolobophora fœtida*) and the planaria, in which organizations certain tissues are regenerated after apparent complete destruction. The destruction is, however, not complete in such cases because the normal regenerative power resides in other cells, which, by the process of metaplasia, build up tissues they do not form in the normal sequence of evolution.
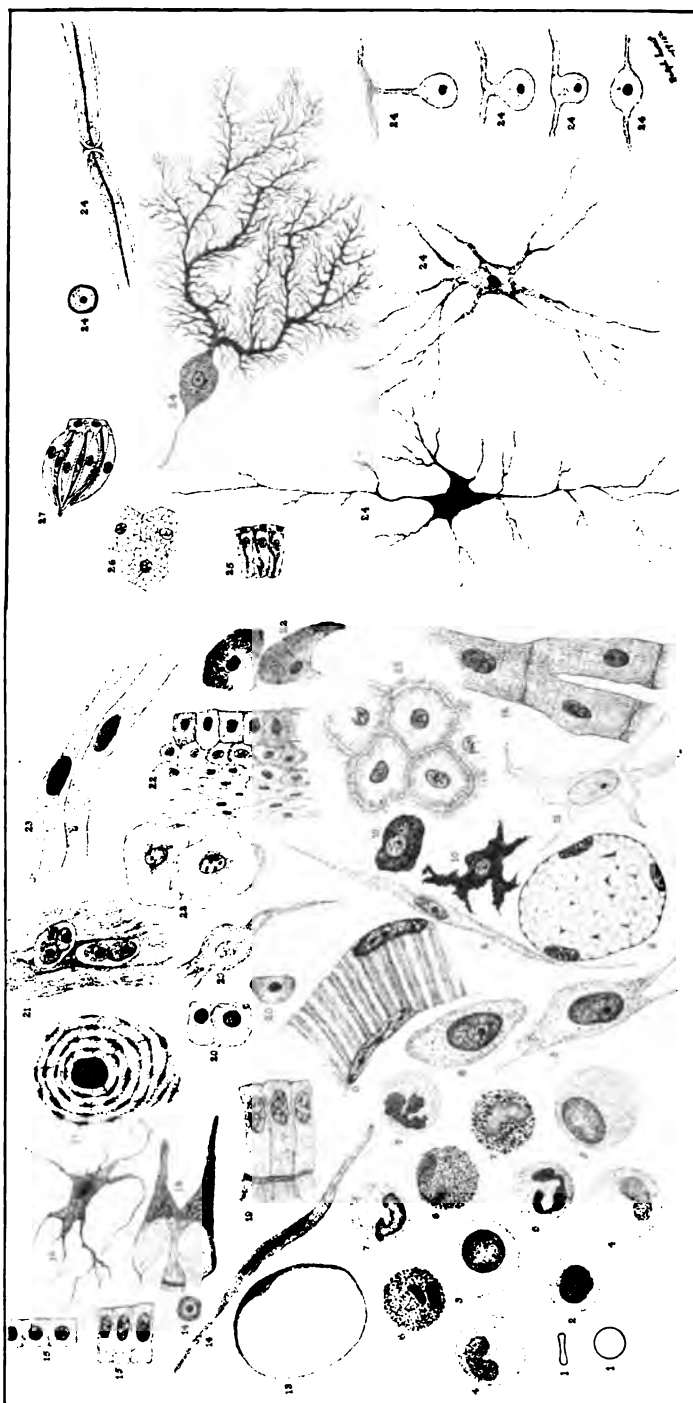
Fig. 325.

tion and differentiation. One finds, therefore, this regenerative factor
a variable and unequal quantity among tissues of the human body.
The protective tissue cells (epitheliocytes) of the skin, for example, are
readily regenerated if not completely destroyed over a large area; the
cells of the retina in all probability are never regenerated even after partial destruction. Fibrocytic, erythrocytic, epitheliocytic, and leukocytic tissues in all probability represent types, the special functions of which show the highest degrees of regeneration.

PRIMARY CYTOPLASIA

- - - - - - Textocytes
- - - - - Textoblasts

SECONDARY CYTOPLASIA

- - - - Textocytes
- - - - Textoblasts

TERTIARY CYTOPLASIA

- - - - Textocytes
- - - Textoblasts
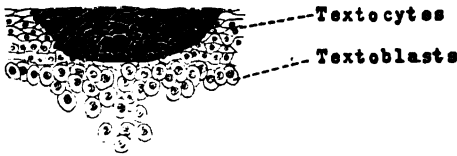
Fig. 327.—Three diagrammatic histologic stages of
reaction of textoblasts of the epithelium of the skin under
normal and certain destructive conditions. (a) Normal
epithelium showing the relative position of textocytes and
textoblasts. (b) Destruction of the textocytes is indicated
by the shaded portion. The response to chronic destruc-
tion is an hypertrophy or an hyperplasia of the textoblasts.
This hyperplasia takes place with and without differenti-
ation into textocytes, depending on the degree and chron-
icity of the destruction. In this condition it is impossible
to state from the morphologic appearance whether the
cells will become differentiated or remain undifferentiated.
(c) Represents the stage of migration of the hyperplastic
undifferentiated textoblasts.

In many tissues of the body coincidentally to normal communistic activity there is constant or periodic normal destruction, with constant or periodic regeneration, both of which depend on communistic functional activity and a constant or periodic destructive action of antagonistic agents. The amount of regeneration depends on the amount of destruction which depends on the quality, quantity, and duration of action of the destructive agent or agents.

Tissue-destruction and regeneration were made the subject of investigation by the writer in the protective cells of the human skin (Fig. 327) and in the secretory epithelium of the human mammary gland (Fig. 328). One finds in these organs that some unknown irritant or irritants of an apparent low degree of virulence, acting over a prolonged period of time, produce certain reactive cellular phenomena; there is first a destruction of the specialized and differentiated cells (textocytes). This destruction is associated with an hypertrophy of

the so-called basal cells (cells of the stratum germinativum, or texto-blasts) and a lymphocytic infiltration in the supporting stroma.

I shall not consider here the factor of lymphocytic infiltration. The hypertrophy of the so-called basal cells, however, is of great impor-tance from the standpoint of the subject under consideration.

One sees clearly that nature, in building up the specialized and differ-entiated protective cells of the skin and the secretory cells of the mammary gland, has also made pro-vision for an anticipated destruction, an antici-pation which is no more remarkable in nature than that of the butter-fly, which deposits its eggs in a safe place and dies with the inherent as-suredness that the eggs will some day develop into caterpillars and eventually into butter-flies, to continue the ex-istence of the kind. In the case of the cells of the skin and the mammary gland, if the irritant is removed, complete re-generation of differen-tiated or specialized cells takes place provided the basal cells them-selves have not been completely destroyed.
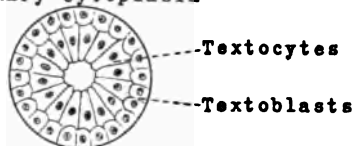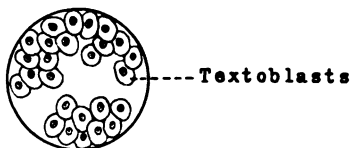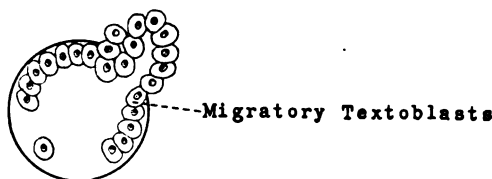
Fig. 328.—Diagram showing primary, secondary, and tertiary mammary adenocytoplasia.

Continuance of the action of the destructive agent or agents produces hypertrophy, hyperplasia, and migration of the basal or regenerative cells (Figs. 327 and 328). Coincidentally with such a hyperplasia the basal cells (textoblasts) do not always become differentiated to the form of the specialized squamous or secretory cells, according to their com-munistic normal foreordination; they retain their oval or spheroid form, become larger, and produce a massed overgrowth of undifferenti-

ated cells (Figs. 327 and 328). The degree of hyperplasia and migration varies under different and perhaps the same irritative circumstances, depending on inherited variable factors in the basal cells, the neighboring tissue-cells, their food supply, natural drainage, and perhaps some unknown factors. The significant biologic facts rest in the attempted cellular regeneration by hypertrophy and hyperplasia, and the effort to change environment by migration, all of which may be seen not only in the breast and skin, but also in the specific cells of the hair-follicle, prostatic gland, and stomach (Figs. 329, 330, and 331).

PRIMARY CYTOPLASIA

Textocytes
Textoblasts

SECONDARY CYTOPLASIA

Textocytes
Textoblasts

TERTIARY CYTOPLASIA

Textocytes
Textoblasts
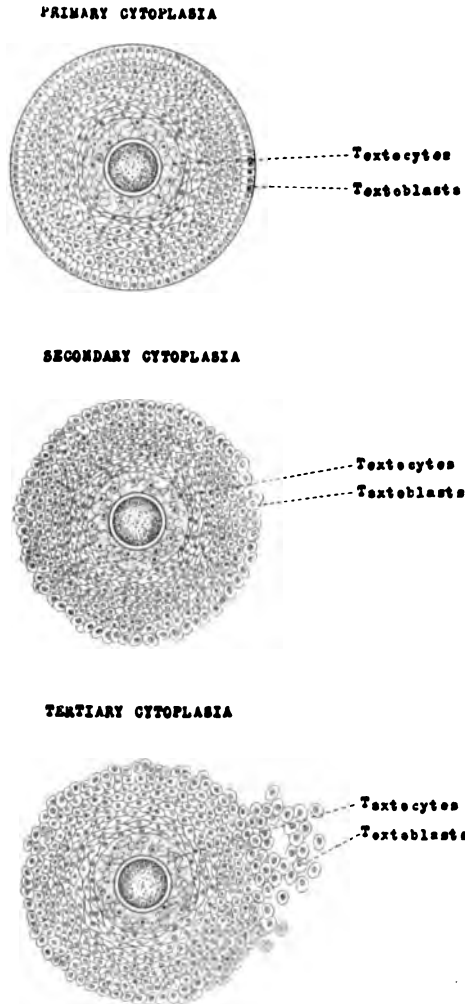
Fig. 329. The reaction to destruction of textocytes in the hair-follicle. A, Primary pilocytoplasia. B, Secondary pilocytoplasia. C, Tertiary pilocytoplasia.

PRIMARY CYTOPLASIA

Textocytes
Textoblasts

SECONDARY CYTOPLASIA

Textoblasts

TERTIARY CYTOPLASIA

Textoblasts
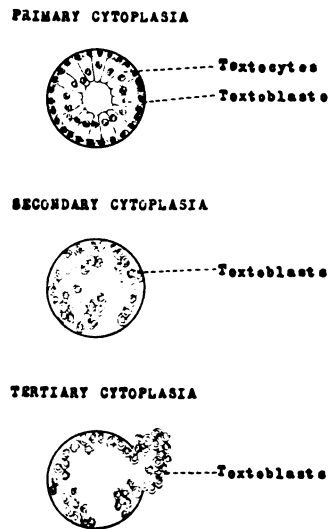
Fig. 330.—The reaction to destruction of textocytes in the prostatic acinus. A, Primary adenocytoplasia. B, Secondary adenocytoplasia. C, Tertiary adenocytoplasia.

A change of environment through overgrowth or migration often stimulates or allows an attempt at differentiation into the specific tissue-cells for which the original reserve or regenerative cells (textoblasts)

were apparently foreordained in the normal evolution of tissues. This is evident in cancerous new-growths which have migrated into other tissues, and in regional lymphatic glands which are the favorite locations of environmental change for such migrants.

Cellular regenerative reaction takes place in one or both of two ways: There is hyperplasia with or without differentiation. A hyperplasia with differentiation into specific tissue-cells may be called textotypic, in contradistinction to that without differentiation, which may be termed cytotypic. This occurs before and after migration.

According to writers on the subject of cancer the principal criterion for the denotation of a condition by this term consists of the destructive

PRIMARY CYTOPLASIA   SECONDARY CYTOPLASIA   TERTIARY CYTOPLASIA

Textocytes   Textoblasts   Textoblasts

Textocytes   Textoblasts   Textoblasts
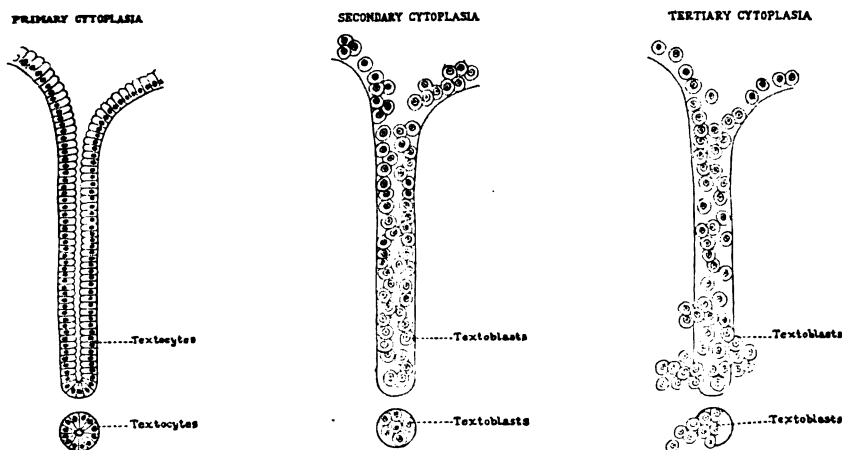
Fig. 331.—The reaction to destruction of textocytes in the gastric tubules. A, Primary adenocytoplasia. B, Secondary adenocytoplasia. C, Tertiary adenocytoplasia.

migration of tissue-cells. Such neoplasms have been often considered to be direct derivatives of tissue-cells because their cells sometimes resemble those of specific tissues of organs from which they have arisen. As a matter of fact, the malignant neoplastic cells (neocytes) do sometimes resemble the specific tissue-cells of the site of origin, but this is not evidence that the tissue-cells themselves have been converted into the cells which at best never are morphologically and functionally identical with the original tissue-cells.

According to the observations of the writer, the cells which constitute cancer are the progeny of the partially differentiated or reserve cells (textoblasts), which have for their natural communistic function the

protective restoration of the specific tissues when the latter have been destroyed. It may be asked, how can a condition which will certainly destroy the whole organism be the result of a protective principle? This perfectly natural question can be answered only by stating a general principle in biology, namely, that regenerative changes do not always consider the communistic adaptation of the whole organism. It is a manifestation of a principle which is inherent in cells, cytologic life being primary, and tissue or organic life secondary. Thus, the planarian, in response to certain stimuli, produces a new head when it already possesses one; the actinian produces a new mouth on the side of its body, under certain regenerative conditions. Protective migration of animals as a result of food famine not infrequently leads to their complete destruction.

In the case of the human being there is no more fitting example of a fatal, protective communistic action of cells than that which occurs when he obtains a severe and destructive burn about the mouth or in the esophagus. Under such circumstances the fibroblasts in the region become hypertrophic, hyperplastic, differentiated, and specialized into dense, contracting scar tissue, which, if the destruction has been great enough, may, as a communistic, regenerative, protective process, inherent in the fibroblasts, completely close the orifice of the mouth or esophagus, the result of which is starvation and destruction of the whole organism. The fibroblast's evolutionary duty in the communism is that of replacing losses of other tissues, and the duty is performed in this incidence at the expense of its own life and the life of the organism. Thus it may be seen that the communistic life is secondary to the life of the cells, even in such a wonderful and complex organization as the human body.

The hyperplasia or neoplasia does not even have to be migratory from a cellular standpoint to destroy the whole organism and thereby be clinically malignant, a term which has been utilized by the medical profession largely to differentiate cancer from other neoplastic conditions generally conceived of as benign. Thus a fibroid tumor of the uterus may be clinically malignant, and still not show cytologic signs of the malignancy so characteristic of cancer.

Biologically speaking, protection may be divided into types: Cytotypic, textotypic, organotypic, systemotypic, organismotypic, familiotypic, raciotypic, speciotypic, etc. Cancer represents the cytotypic protection which is of primary importance in all protection of living protoplasm.

From a biologic standpoint, the three reactions of regenerative cells of tissues to antagonistic influences are hypertrophy and hyperplasia with differentiation, hyperplasia without differentiation, and hyperplasia with migration, with or without partial differentiation. These three conditions have been termed cytoplasias (conditions of cells) and have been numerically classified by the writer as primary (restauro-), secondary (expando-), and tertiary (migro-) cytoplasia. This classification is applicable to the regenerative cells of epithelial tissue of the mammary gland, prostatic gland, skin, hair-follicle, stomach, fibrous connective tissue, erythrocytic tissue (red blood-corpuscles), and lymphocytic tissue. These represent eight tissues out of possibly twenty-seven known specific tissues in the human body. Doubtless, there are other specific tissues in the human economy and perhaps some of those already mentioned may be eventually divided into other specific tissues. In all the following tissues, adenotex, cardiomyotex, chondrotex, endotheliotex, epitheliotex, erythrotex, fibrotex, leukotex, leiomyotex, lipotex, lymphotex, melanotex, myxotex, neurotex, osteotex, pilotex, rhabdomyotex, and tendotex, with the exception of the neurotex and perhaps the myotex, the fact has been demonstrated that all are regenerated after loss, the degree of regeneration varying considerably in the human body.

The following classification of the three biologic reactive phenomena which take place in the regenerative cells of tissues may be made:

Primary (restauro-)	adeno- cardiomyo- chondro- endothelio- epithelio- erythro- fibro- leuko-	
Secondary (expando-)	leimyo- lipo-	cytoplasia
Tertiary (migro-)	lympho- melano- myxo- neuro- osteo- pilo- rhabdomyo- tendo-	

Such a nomenclature of known reactive facts has served the writer as a convenient, simple, and practical biologic, histologic, and clinical terminology. The writer does not mean that these terms should be utilized to designate neoplasms. They apply only to the tissue reaction, which is, after all, the essential thing to be considered. Animal and vegetable neoplasms represent only phases of such reaction.

From a clinical standpoint, a hypertrophy and hyperplasia, with complete tissue differentiation (restauro-cytoplasia), represents tissue regeneration, which is a benign condition since it is normally reconstructive from a communistic standpoint instead of destructive. A hyperplasia without tissue differentiation (expando-cytoplasia) represents a condition of the cells in which no one can foretell whether the cells will become differentiated into tissues, and thereby be constructive, or migrate and become destructive.

Such a condition is, therefore, in the presence of science, a questionable condition. Its benignancy or malignancy, in so far as the organization is concerned, with our present knowledge, cannot be forecast. The probability of possible migration may be suspected from the frequent morphologic identity of these undifferentiated cells to the migratory cells of a known malignant or cancerous condition, the only difference being their location.

Biologically considered, primary cytoplasia represents a tissue regenerative condition, the secondary cytoplasia represents a neoplastic condition, and tertiary cytoplasia represents a neoplastic migration to regions foreign to the cells in question. The whole field of tissue replacement, tissue regeneration, and benign and malignant (cancerous) neoplasms (new-growths) is comprehended in these three groups.

The following diagram represents the relation of malignant (cancerous) and so-called benign neoplasms to the evolution and organization of the human body:

```
Fertilization        (Ovocyte and spermatocyte)
    |
Segmentation            (Protextoblasts)
    |
Prodifferentiation*        (Textoblasts)
         /        \
Differentiation        Neoplasia (undifferentiation neocytes)
(Textocytes)                (Benign? or malignant?)
              \              /            \
   Differentiation (Textocytes)      Migration (neocytes)
      (Benign neoplasms)            (Malignant neoplasms)
                        \              /            \
        Incomplete Differentiation        Undifferentiation (neocytes)
(Less malignant)    (Pseudotextocytes)      (More malignant)
```

* The stage of prodifferentiation exists prenatally and postnatally and may be distinguished terminologically by calling the prenatal cells of segmentation protextoblasts and the regenerative postnatal cells textoblasst.

Briefly, in conclusion, the writer makes the following generalizations from his experience in his studies of cancer's place in general biology:

1. All multicellular organisms represent communisms of cells which have divided their labors and become specialized and differentiated to form tissues.

2. Nature has provided for the regeneration of most, if not all, tissues when the tissues are partially destroyed by antagonistic forces.

3. In many animal and vegetable tissues the regenerative cells respond to tissue destruction in three degrees, that is, hypertrophy, hyperplasia, and migration.

4. During hyperplasia with or without migration the cells sometimes attempt to differentiate.

5. Limited hyperplasia with complete differentiation produces tissue regeneration. Unlimited hyperplasia without complete differentiation produces the so-called malignant neoplasms.

6. Cancer represents an unlimited hyperplasia of regenerative cells of tissues plus migration without complete differentiation.

7. Regeneration (hyperplasia) without differentiation is a cytotypic protective process.

8. Regeneration (hyperplasia) with differentiation is a textotypic protective process.

9. Cancer is a cytotypic instead of a textotypic protective process.

10. In nature cytotypic protective processes are sometimes fatal to the communism of which the reactive cells are a part.

11. All the reactions may be designated by a simple biologic terminology which standardizes clinical, histologic, and biologic facts.

REFERENCES

MacCarty, W. C., and Willis, B. C.: Carcinoma of the breast. Old Dominion Jour. Med. and Surg., 1911, xii, 189–198.

MacCarty, W. C., and Blackford, J. M.: Involvement of regional lymphatic glands in carcinoma of the stomach. Ann. Surg., 1912, iv, 811–843.

MacCarty, W. C., and Sistrunk, W. E.: Benign and malignant ovarian cysts. Surg., Gynec. and Obst., 1913, xvii, 41–50.

MacCarty, W. C., and Broders, A. C.: Chronic gastric ulcer and its relation to gastric carcinoma. Arch. Int. Med., 1914, xiii, 208–223.

MacCarty, W. C.: The histogenesis of cancer of the breast and its clinical significance. Surg., Gynec. and Obst., 1913, xvi, 441–459.

Clinical suggestions based on a study of primary, secondary (carcinoma?) and tertiary or migratory (carcinoma) epithelial hyperplasia of the breast. Surg., Gynec. and Obst., 1914, xviii, 284–289.

The histogenesis of carcinoma in ovarian simple cysts and cystadenoma. Collected Papers, Mayo Clinic, 1913, v, 380–390.

MacCarty, W. C., and McGrath, B. F.: The frequency of carcinoma of the appendix. Ann. Surg., 1914, lix, 675–678.

'17—52

MacCarty, W. C.: The biological position of the carcinoma-cell. Pan.-Am. Surg. and Med. Jour., 1915, xx.

Precancerous conditions. Jour. Iowa State Med. Soc., 1914–15, iv, 1–11.

The histogenesis of cancer of the stomach. Am. Jour. Med. Sc., 1915, cxlix, 469–476.

Notes on the regularity and similarity of cancer cells. Collected Papers, Mayo Clinic, 1914, vi, 600–602.

New facts about cancer and their clinical significance. Surg., Gynec. and Obst., 1915, xxi, 6–8.

Irwin, H. C., and MacCarty, W. C.: Papilloma of the gall-bladder. Ann. Surg., 1915, lxi, 725–729.

MacCarty, W. C.: Evolution of cancer. Collected Papers, Mayo Clinic, 1915, vii, 903–917.

Broders, A. C., and MacCarty, W. C.: Melanoepithelioma. A report of 70 cases. Surg., Gynec. and Obst., 1916, xxiii, 28–32.

MacCarty, W. C.: Facts versus speculation in the professional conception of cancer. Texas State Jour. Med., 1915, xi, 165–169.

A new classification of neoplasms and its clinical value. Am. Jour. Med. Sc., 1916, cli, 799–806.

MacCarty, W., and Mensing, E. H.: The relation between chronic mastitis and carcinoma of the breast. St. Paul Med. Jour., 1916, xviii, 164–167.

GRADUATE WORK IN MEDICINE IN THE UNIVERSITY OF MINNESOTA*

L. B. WILSON

INTRODUCTION

Graduate and research work in pathology, clinical medicine, and surgery has been carried on at Rochester in the Mayo Clinic for several years. In 1912 definite three-year courses in these subjects for graduates in medicine were instituted. In 1914 the University of Minnesota, through its Medical School, began graduate work in the various fields of medicine and surgery in addition to that which had already been offered for some time in the laboratory branches. In June, 1915, the University and The Mayo Foundation entered into an agreement by the terms of which the funds of the Foundation were devoted, under direction of the Board of Regents of the University, to graduate and research work in medicine. The first arrangement was for a temporary period. On September 13, 1917, the agreement was made permanent. By the terms of this agreement the University of Minnesota has entire control of the funds of The Mayo Foundation and of the graduate medical education and research of the Foundation. Until such time as the funds of The Mayo Foundation shall have reached the sum of two million dollars by the addition of accrued interest, all the current expenses of the Foundation shall be borne by the Mayo Clinic. On September 13, 1917, The Mayo Foundation fund amounted to $1,650,344.79. For the fiscal year ending July 31, 1917, the expenditures of the Foundation were $140,365.25, exclusive of "overhead," i. e., rent, heat, light, etc.

The affairs of all the graduate work in medicine in the University are controlled by a committee of eleven men, consisting of the President of the University, the dean of the Graduate School, the dean of the Medical School, and the director of The Mayo Foundation, ex officio, and of four appointive members from the Medical School and three appointive members from The Mayo Foundation.

GENERAL PLAN

1. *Object.*—The graduate work in medicine on The Mayo Foundation and most of that in the University at Minneapolis is not intended for those seeking brief practitioners' or review courses. Opportunities for work of this kind are to be found in the summer session of the Medical School and in the courtesies extended to visiting physicians and surgeons in the Mayo Clinic. The object of the University of Minnesota is to place graduate work in medicine on a university basis. By this is meant the placing of advanced graduate medical education on a basis comparable with that of graduate education in the arts and sciences in other departments of universities of high standing. The formal rules and regulations for the guidance of the work have had their origin in the rules and regulations which govern graduate training in subjects other than medicine. Material modifications of these rules and regulations will probably be made—for example, the language requirement for students in clinical branches has been the subject of much discussion. Again it may become recognized that recent graduates of Class A medical schools already have a scientific training approaching that held by the possessors of the Ph.D. degree,[*] and some modification of the graduate degree granted them may be accordingly made.

2. *Entrance Requirements.*—Entrance upon the work for the degree of Ph.D. in medicine in the University of Minnesota is limited to those who have—(a) the Bachelor's degree or its equivalent; (b) the degree of Doctor of Medicine from acceptable institutions (that is, those in Class A of the American Medical Association); and (c) one year's experience as intern in an approved hospital, or as an assistant in a laboratory in an acceptable medical school. In the fundamental laboratory sciences (anatomy, physiology, bacteriology, pathology, and pharmacology) properly prepared students may be admitted without the possession of the degree of Doctor of Medicine, and, of course, without the internship, as candidates for the Master's degree (M.A. or M.S.) or the unmodified Doctor's degree (Ph.D.).

3. *Course Requirements.*—For the Doctor's degree (Ph.D.) at least three full years of successful graduate study are required; for the Master's degree in the laboratory sciences a minimum of one year of residence is required. Each student registers for a major and a minor subject,

[*] Wilson, L. B.: The Status of the Graduate Degree in Medicine. Science, 1917, xlvi, 127–131.

the minor supporting the major. Each student takes both written and oral examinations in his minor and in his major subject, and before graduation presents a thesis in his major subject which he must further defend in an oral examination before the entire staff of the department in which he is taking his major. This examination also includes questions in any portion of the field of the major.

4. *Degrees.*—On the satisfactory fulfillment of the requirements the candidate is recommended to the Board of Regents as a proper recipient of a graduate degree. In June, 1917, the University granted the following graduate degrees in medical branches:

> Taylor, R., Doctor of Science (in Pediatrics).
> Woltmann, H. W., Doctor of Science (in Neurology).
> McWhorter, G. L., Doctor of Philosophy (in Surgery).
> Morris, R. E., Doctor of Science (in Medicine).
> Stewart, C. A., Doctor of Philosophy (in Anatomy).
> Crispin, E. L., Master of Science (in Medicine).
> McMahon, F. B., Master of Science (in Surgery).
> Drips, Della G., Master of Science (in Pathology).
> Pettibone, Dorothy, Master of Science (in Bacteriology).
> Gault, C. C., Master of Arts (in Physiology).
> Kittelson, J. A., Master of Arts (in Anatomy).
> McKinley, J. C., Master of Arts (in Anatomy).

FACILITIES

1. *Living Stipends.*—The stipends to be paid Fellows in the Graduate Medical School of the University this year aggregate about $50,000, $10,000 of which is for fellowships in the Medical School of Minneapolis and $40,000 for fellowships at Rochester. At Minneapolis these fellowships pay $500, $750, and $1000 per year for the first, second, and third years respectively. At Rochester the first year's stipend is $600, and the second and third years the same as at Minneapolis.

While these stipends are small, they enable the graduate student to pursue his work with less worry than would fall to his lot were he earning his way. The regular course of training in medicine is longer than that given in any other profession. To add to this training three years more of special preparation without providing some means of living would work an injustice to students in moderate circumstances. Fellowships, therefore, are a necessity for the great majority of students continuing their study after their regular intern service.

2. *Libraries.*—The general medical libraries on the Campus in Min-

neapolis and in Rochester contain complete files of most of the important medical periodicals. The work in these libraries is under the direction of a corps of well-trained and enthusiastic librarians and bibliographers. A good library, well stocked with complete files of the leading medical periodicals, is an absolute necessity in graduate work in scientific medicine. While meager libraries may be eked out by the generous assistance of the Surgeon-General's library, the student of scientific medicine must have the opportunity to make himself thoroughly at home in a well-stocked and well-arranged library. Not less important than the books, however, are trained assistants. Many young medical graduates need help in learning to use their time intelligently and efficiently in the modern library. Of course, the librarian and bibliographer should assist the graduate student rather than do his work for him.

3. *Laboratories.*—Well-equipped laboratories in the fundamental medical sciences (anatomy, chemistry, physiology, pathology, etc.) and as adjuncts to the clinical branches are amply provided both in Minneapolis and in Rochester. Extensive and carefully cataloged research museums and well-equipped departments for experimental work are also at hand in both places. The graduate student must have the best of modern laboratory facilities for pursuing his investigations, not only in the basic medical sciences, but also concerning tissues, body fluids, and physiologic and pathologic processes in direct relationship to the individual patient.

4. *Hospitals.*—More than 1000 hospital beds furnish the clinical material for the graduate students of the University of Minnesota. Two hundred of these are in Minneapolis and 800 in Rochester. The graduate student must have the facilities at hand for studying his patients under orderly hospital care.

5. *Ambulatory Patients.*—At the University in Minneapolis and at the Mayo Clinic in Rochester between 55,000 and 60,000 ambulatory patients are examined annually. The graduate students must have opportunity to examine for diagnosis a large number of patients. By preference these should be referred cases, since this group contains a high percentage of patients with diseases difficult of diagnosis.

6. *Incentive to Investigation.*—In the Medical School at Minneapolis and in The Mayo Foundation and Clinic at Rochester, a number of high-grade men, members of the faculty or permanent staff, are devoting the whole or a large share of their time to the advancement of medical science in the fundamental and practical fields. This, I believe, con-

stitutes the most important agency in the development of the Graduate School, since it supplies the inspiration, encouraging graduate students to do scientific medical work. If the members of the staff of a graduate school are doing only mediocre routine work, the graduate student is apt to do only mediocre work. If they are doing routine work of a high order, the student will do routine work of a high order. If, in addition to high-grade routine work, they are doing high-grade investigative work, fundamental or clinical, the graduate student is almost certain to shape his ideals and his work in accordance with their inspiring example.

Personnel of the Student Body

1. *Source and Number.*—During the past year graduate students in medicine have been received from the following medical schools: Atlanta College of Physicians and Surgeons, Calcutta, Colorado, Columbia, Edinburgh, George Washington University, Harvard, Jefferson, Johns Hopkins, Ludwig-Maxe University (Munich), Marion Sims, Marquette, Maryland, Michigan, Minnesota, Nashville University, Nebraska, Northwestern, Pennsylvania, Rush, St. Louis, Toronto, Tulane, Vanderbilt, Virginia Medical College, and Virginia University.

Enrolment in medical departments—118.

	Rochester	Minneapolis	Total
Enrolment in Clinical Departments (by majors):			
Surgery	58	3	61
Ophthalmology and Otolaryngology	3	4	7
Medicine	11	2	13
Nervous and Mental	0	2	2
Pediatrics	1	4	5
Obstetrics and Gynecology	0	2	2
Total	73	17	90
In Fundamental Departments:			
Anatomy	0	9	9
Pathology	4	0	4
Bacteriology	6	6	12
Physiology and Physiologic Chemistry	0	3	3
Total	10	18	28
Grand Total	83	35	118

2. *Weak Points in Preparation.*—As these young men come to us, we find most of them well prepared to be general practitioners. This preparation has been the highest aim of most medical schools, and is that required by state examining-boards. The graduates, as a rule, are well grounded in the fundamental medical sciences, and have had good elementary training in all of the clinical subjects. The most frequent scholastic defects are lack of general information, poor training in the use of the English language, little efficiency in the use of a library, no great ability in attacking intensively problems of research, lack of well-organized procedure in history-taking, and little conception of means of correlating their clinical observations with those of others.

3. *Object in Doing Graduate Work.*—Their objects at entrance are indicated by the facts that of the 118 graduate students, 28 are taking work in some of the fundamental departments for their majors, while 90 are taking work in the clinical departments for their majors. In the fundamental departments there are 9 in anatomy, 3 in physiology, 4 in pathology, and 12 in bacteriology. In the clinical departments, 61 are in surgery, 13 in medicine, 7 in ophthalmology and otolaryngology, 5 in pediatrics, 2 in nervous and mental diseases, and 2 in obstetrics and gynecology. These enrolments indicate the primary incentives of the students in taking graduate work. Some of the students are only preparing themselves to earn a better living. A fair percentage of them add to this motive the desire to acquire special knowledge in their chosen fields for the sake of the patient. A few are actuated mainly by the latter motive. It is noteworthy that many who begin graduate work with no other apparent desire than that of increasing their earning capacity by becoming good mechanics in some branch of medicine are later inspired to take up some fundamental or clinical problem and pursue it with real zest. Not infrequently men ask to be left a longer period on some service which gives them a better opportunity for investigative work, or to be directly transferred to such a service. Problems in surgery and in clinical medicine, especially in the fields of metabolism, cardio-vascular disease, etc., have engaged the attention of a number of our best young men. The departments of physiologic chemistry, bacteriology, pathology, and anatomy also contain a small number of enthusiastic students. While several men have changed their majors from surgery to medicine, only one so far has changed his major from medicine to surgery; and that was done on the advice of his instructors when the

student revealed a phenomenal knowledge of anatomy and an aptitude for minute dissections.

UNIVERSITY IDEALS

In a democratic university owned by the people and managed to serve the people, all forms of physical and mental training may be proper. Even the purely trade school now has its recognized place in university training. So, in medical training, technicians, general practitioners, and specialists in the various practical and fundamental branches may all properly be trained by the university. The girl who wishes to remain a mere technician, a preparer of microscopic sections, for example, may be given an equal opportunity with the man who wishes to spend his life in surgery. The country practitioner who wishes to brush up for three weeks on any medical subject or subjects may, quite as properly, be given an equal opportunity with the man who wishes to spend three years in investigating beriberi. On broad grounds there can be no objection to any or all of these subjects receiving their due share of attention. But, while admitting all this to be true, we must not lose sight of the fact that the university has also an important duty to perform in determining an individual's fitness for beginning a certain piece of work and in setting standards by which the work shall be measured if it is to receive any stamp of approval from the university. In other words, the university, besides furnishing opportunity for study, must standardize its output. And it is equally true that in graduate work in medicine the unprepared student who takes a short course in a purely technical subject, the graduate student who takes, however long, a course which develops his efficiency only, and the graduate student with a well-trained mind who spends years in advancing the science, as well as the art, of a specialty, should not be measured by the same standard nor stamped with the same label at graduation.

For years more or less well-organized formal instruction to graduates in medicine has been given by many schools in the United States as well as abroad. The difference between such work and that which the University of Minnesota is now doing is that too frequently the former was a "stuffing" process for financial gain, while the latter is an attempt to furnish gratis the organized facilities by which the student may work out his own salvation. These graduate students of medicine are making a prolonged and serious effort to increase their efficiency and to add to

scientific knowledge in certain fairly limited fields. The University of Minnesota provides the facilities and measures their achievements.

In starting on this work, the University of Minnesota felt that its safest course was to proceed from the customs which had hitherto obtained in graduate work in non-medical subjects in universities generally. It realizes, however, that the rules which govern the standardization of graduate work in literary subjects do not cover satisfactorily the variety of opportunities asked for by many earnest and honest graduate students in medicine. The problem of the readjustment of these rules is one which no university can settle for itself. There must be uniformity of standards among the universities providing graduate training and granting graduate degrees in medicine in the United States. Such uniformity was contemplated by the Association of American Universities at its meeting last winter when it requested the Educational Council of the American Medical Association to appoint a committee, of which a majority of the members were present, to confer with them concerning graduate degrees in medicine. However, until the universities do take uniform action, there seems to be no safety in any course other than that of granting certificates of attendance except for such work as adheres to the rules already obtaining in the granting of the Master's and Doctor's degrees in non-medical sciences.

MEDICAL JOURNALS FROM THE STANDPOINT OF THE CONTRIBUTOR*

MRS. M. H. MELLISH

My official position of buffer between contributors to and editors of medical journals does not lend itself readily to an unrestrained discussion of this topic. If it were not that the medical editor is so often the medical publisher as well, I should find myself always in sympathy with the editor. The editor, confronted with many and varied manuscripts, with very little time in which to reduce them to law and order, unfortunately is often misinterpreted in his efforts to secure the best results with the least possible friction and delay. The contributor is very apt not to appreciate the reasons for the revision. Indeed, the opinion seems universal among writers that many of the rules and regulations regarding the editing and publishing of papers are both perplexing and inconsistent. It would seem that editors and publishers are not generally aware that many of their contributors would gladly coöperate with them in bringing about some form of standardization which would cover at least a few general rules and permanently settle various unimportant though harassing details in relation to so-called printer's style.

Assuming that the writer is capable of grouping his ideas clearly and logically into sentences and paragraphs, and that he has in mind a definite plan for the construction of his paper in keeping with the material in hand, there is, nevertheless, a chance that his plan will not meet the requirements of the journal to which his article is sent. If the article is accepted for publication, the shock to the writer in finding how far his ideals differ from those of the editor does not come until the proof is received. He may then find a changed title, inserted or revised headings, transposed paragraphs, tabulated statistical data pulled down and put into the text, or vice versa, and innumerable minor corrections. If the contributor is good natured and is conscientiously trying to improve his

writings, he accepts these arbitrary changes with more or less gratitude, and determines to profit by them in the preparation of papers in the future. The obvious happens; his next manuscript comes back in the form of galley-proof from some other representative journal in still another puzzling transformation; and he may repeat this experience with each of the "57 varieties" of medical journals, the editors of which all claim individual rights in the matter of style.

In order to prevent these constant misunderstandings it should be possible, by joint conference between representative contributors, editors, and publishers, to adopt certain general rules. The following are suggested as examples of such rules as might be considered and adopted:

1. Titles should indicate clearly to the reader and bibliographer the matter within. Much valuable material is lost to investigators because the titles used are nothing but vague generalities, and, therefore, can find no proper place in the current indexes.

2. Bibliographies should give each author's name and initials, the title of the article, the name of the periodical in which it appeared, the year of publication, the volume number, and the inclusive paging. Particular emphasis should be placed on the inclusive paging, as it is a matter of considerable importance to the reviewer to know the length of an article. In this connection it might be suggested also that, when only an abstract has been read, the writer, in referring to it, should, in all fairness, make reference to the abstract rather than to the original article from which entirely different conclusions might have been drawn.

3. Uniform rules should be made for main headings, subheads, abbreviations, numerals, etc. One able editor writes "$1\frac{1}{2}$ inches" in figures, another insists on spelling it out, and a third, equally eminent, compromises by using both forms in the same sentence.

4. Foreign words and phrases should be abandoned when the English substitute will serve the purpose as well or better, and Latin and Greek plurals and diphthongs should be discarded.

5. Italics for emphasis should be excluded, and their use for such foreign words as may not be discarded should be minimized. Italics in English and their substitute, the wide spacing of the letters of a word, so common in German literature, equally insult the intelligence of the reader.

6. A standard size, or, at most, two standard sizes, of page forms for medical journals should be adopted. Contributors like to know how many pages their manuscripts will make. They would like also to be

able to arrange their own tabulations, charts, etc., before sending them in for publication. All drawings and photographs could be made to correspond to one or the other of the two sizes, and would not lose value in the reductions sometimes necessary in order to accommodate them to the page.

Why would it not be possible to give the writer an idea of the approximate date on which his article will be published? The indefinite postponement of the publication of his paper for months after it has been submitted constitutes the chief grievance of the contributor against the editor and publisher; and it is a real grievance in these days when priority of publication is accepted witness to the priority of research results. To affix the date on which the article was submitted for publication is not adequate compensation.

In this age of standardization it would seem that the Medical Editors' Association might adopt some standard of medical publication. As example of what may be done in even a short time, we have the recent work of the committee on standardization of drugs, reagents, instruments, and apparatus of the Medical Section of the Council on National Defense. It would be interesting to know just how far this revision was stimulated by enforced attention to the ponderous and impractical supply lists made many years ago, but now quite obsolete. It is to their credit that this committee apparently did not attempt to choose from the old lists in making the new ones. They reverently shelved them, and substituted a list much shorter and better suited to present-day purposes. In a similar manner differences of opinion regarding rules for publication might be settled by a committee of contributors, editors, and publishers of medical literature. If such a committee could view the many differences, variations in style, etc., in their conglomerate mass, it is more than probable that they, too, would be willing to cast them all aside and begin anew.

Another important and disputed question concerns the extent of the editing of the individual contribution. We all know that, having grasped the plot in a badly worded manuscript, it is much simpler to rewrite it according to our own version and conceptions than it is to put these in the background and laboriously follow the argument in its original form, keeping in mind the writer's point of view and preserving his legitimate right to tell his own story in his own way. Here the editor's zeal for brevity is apt to intrude. The relation of brevity to literary style in medical literature is worthy of consideration. It is un-

questionably true that good literary style in American medical literature is rare. There is, indeed, a marked difference in this respect between the medical papers written here and those written and published in some other countries, for example, England and France. I hasten to antici- pate the argument which I, myself, have used many times, that American physicians are a practical, busy, ambitious, crowding, and hurrying folk who think it is absolutely imperative, in order to satisfy a clamoring public and to advance their own particular ends, to announce their views and their wares without delay. Nor is the fault entirely with the writer. The editor of the progressive medical journal also feels the necessity of supplying his progressive subscribers with the latest thought of as many medical writers as possible. Again the result is obvious; manuscript is returned to the writer with the request that it be reduced to the small- est possible space in order to make room for other papers. The editor may even suggest the manner of reducing it, or, if he has the courage of his convictions, he may delete and transpose it to his own satisfaction and to the bewilderment of the writer.

It would be difficult to draw the line between the contributor's, the editor's, and the publisher's responsibility for the present unliterary quality of American medical literature, but one point must be particu- larly clear to all—that some reform should be instituted: some definite procedure which will enable the writer, the editor, and the publisher to work together for results more in keeping as to dignity and scientific worth with the ability and the independence of men in the American medical profession. It would be well if medical legislation could go fur- ther and limit and classify medical journals. This would enable the writer to determine for himself the best medium of publication for his article. In addition to the fact that many of the journals now in exis- tence are a discredit to the profession, there is also the tragedy that their doubtfully valuable contents are included in our already over- crowded indexes.

With regard to the subject-matter of medical articles: It does not seem possible that editors of medical journals should find it necessary to go on indefinitely publishing so much material that is of little or no value. To the casual observer there seems to be no adequate reason for the edi- torial failure to discriminate between the excellent and the unworthy. Impromptu talks to popular or semi-scientific societies by celebrities, who, importuned to speak without preparation, often restate age-old ideas or improbable hypotheses, should not be sought for publication by

editors and publishers. On the other hand, the details of original investigation should be asked for, and should not be so curtailed or mutilated in publication as to make it impossible to determine the worth of the material. In this respect the custom of German editors might be more nearly approached. Material of such character could be published serially, instead of in a number of disconnected articles in which, though the record of the investigation may be unbroken, the whole problem is not apparent to the reader. Thus when the ideal in the publication of medical literature shall be attained, the investigator will not be obliged to wade through pages of words in order to find one, or not even one, small item of useful knowledge, nor be annoyed by the curtailment of really valuable studies that should be published in detail.

Still moving toward the perfect in medical literature, would it not be practical to publish in each issue of a medical journal short biographies, a "Who's Who," of the contributors to that issue, as is done by the *Atlantic Monthly* and many other good literary magazines? These biographies should contain the author's full name and address, his degrees, medical positions, specialty, etc. The reader would appreciate this, since, at a glance, he might be able to identify the particular "William Jones" writing on appendicitis, and, possibly, to evaluate the article without reading it.

Finally, I would recommend that the American Medical Editors' Association take the initiative in bringing about the appointment of a committee of representative contributors, editors, and publishers whose duty it shall be to further the cause of medical education by standardizing medical literature and medical publications, by discouraging the circulation of low-grade journals, or, if possible, suppressing them, and by the adoption of universal rules which will bring about a more intimate association between contributors and editors.

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